DISS. ETH NO. 23604

THE ROLE OF SENSORIMOTOR TRAINING AND POSTURAL CONTROL IN CHRONIC LOW BACK PAIN REHABILITATION

A thesis submitted to attain the degree of

DOCTOR OF SCIENCES of ETH ZURICH

(Dr. sc. ETH Zurich)

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2016

The role of Sensorimotor Training & Postural Control in Chronic Non-Specific Low Back Pain

Doctoral Thesis

Michael A. McCaskey

"A fool believes that the tallest mountain in the world
will be equal to the tallest one he has observed"
—Lucretius

For my mother, who showed me the path.
For my wife, who kept me on the path.
For my son, who now leads the path.

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Abbreviations

C-JRE	Cervical joint repositioning error
CBRG	Cochrane Back Review Group
CEA/CIA	Confidence ellipse area
CI	Confidence intervall
CM	Centre of mass
CNLBP	Chronic non-specific low back pain
CNS	Centra nervous system
CONSORT	Consolidation Standard of Reporting Trials
CP	Centre of pressure
DOF	Degrees of freedom
EC	Ethical Committee
FU	Follow-up
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICD	International Classification of Disease
ICF	International Classification of Functioning
JDV	Joint deviation vector
LBP	Low back pain
MD	Mean difference
ME	Measurement event
NP	Neck pain
ODI	Oswestry Disability Index
PPT	Postural proprioceptive therapy
PT	Physiotherapy
RCT	Randomised controlled trial
SD	Standard deviation
SE	Standard Error
SEA	Standard error area
SLIT	Sub-effective low intensity endurance training
SMD	Standardised mean difference
SMT	Sensosrimotor Training
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SR	Systematic Review

T0	Pre-test
T1	Post-test
UCM	Uncontrolled manifold analysis
UI	Uncontrolled manifold analysis index
VAS	Visual Analogue Scale for pain
WHO	World Health Organisation
$\hat{\xi}$	Estimated effect size

CHAPTER 1

General Introduction

Motivation

"Society has an obligation to attempt the restoration of function and the reduction of pain. This is based upon both moral principles and upon economic reality."

J.D. Loeser (1999)

I came across these lines during my epidemiological research on low back pain (LBP) prevalence in my early Ph.D. days. I was utterly impressed by this man's ability to compress the importance of pain research, so poignantly, in just two sentences. Pointing out how pain is not an individual problem solved in solitude, but must be addressed with social involvement. Reminding us how chronic pain impairs function, every day. Opening our eyes to the vast economical consequences of an endemic disease in western societies. And finally, daring us not to ignore what cannot be seen, but to look closer and take responsibility. I kept these few words within sight while working on this project as they were the basis of my motivation to investigate one tiny aspect of our societal attempt to restore function and reduce pain.

It is not enough to provide fancy therapies and complicated untenable explanations of possible causes and remedies. We must seek well-founded explanations for the suffering, evidence for the treatment's effectiveness, and ways to monitor improvements and deteriorations of this condition. A qualitative report alone, no matter how professional, is no longer enough to record changes of symptoms after interventions. It must be in the interest of all to search for evidence which underlines the value of a chosen treatment. At the same time, we must reflect on the evidence and be willing to modify treatments in response to new findings.

My background in human movement sciences and year-long, deeply enshrined conviction of the importance of physical activity to maintain a healthy lifestyle has encouraged me to seek black-on-white evidence for my beliefs. Because so much 'belief' was involved, the only way to go about this, was the rigid methodologies of physical activity research in a clinical setting. I was very lucky indeed to find such a professional partner at the Reha Rheinfelden, with its experienced team of researchers and clinicians and excellent facilities. In a joint venture with the institute of Human Movement Sciences at the ETH Zurich, we set out to summarise the evidence of the effectiveness of sensorimotor training (SMT), a specific, non-pharmaceutical intervention in patients with chronic low back pain. We proposed new measures to assess movement aberrations and conducted an experimental trial to assess the effectiveness of this particular treatment. These three iterative phases have delivered incremental knowledge components to contribute to our understanding of low back pain and are presented in Chapter 2 to 5.

Definitions

Three interdependent factors are discussed in relation to SMT, which is the core theme of this research project (Figure 1.1). As these terms are broadly defined in the literature, their meaning

in the context of this thesis are described below.

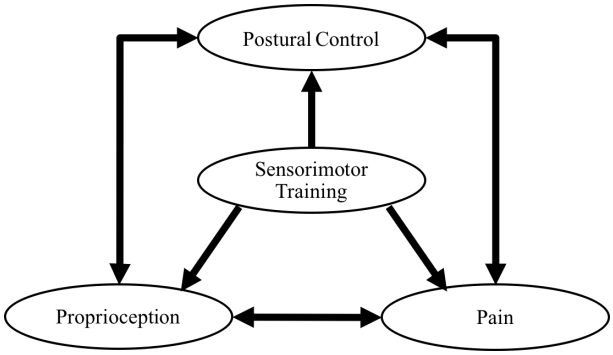

Figure 1.1: Interdependent relationship of topics covered in this thesis

Chronic non-specific low back pain

The World Health Organisation (WHO) defines LBP as "pain and discomfort, localised below the costal margin and above the inferior gluteal folds, with or without referred leg pain" [1]. In this thesis, chronic LBP is further defined as pain persisting for at least 12 weeks or recurring LBP that intermittently affects an individual over a long period of time [1]. Non-specific LBP is defined as LBP not attributed to recognisable, known specific pathology (e.g. infection, tumour, osteoporosis, ankylosing spondylitis, fracture, inflammatory process, radicular syndrome or cauda equina syndrome) [2, 3]. The international classification of disease categorises non-specific LBP as pain (M54.5) with central nervous system sensitivity to pain (G96.8) and persistent somatoform pain (F45.4). Often misunderstood or falsely referred to as a disease, chronic non-specific LBP (CNLBP) is a multifactorial constellation of symptoms with unknown origins [1, 2]. Thus, the international classification of functioning (ICF) is the more appropriate classification system, as it describes the relationships of the condition with body structures and functions but also describes how the symptoms affect daily activity and participation. Powers et al. [4], classified CNLBP as shown in Table 1.1 and provides clinical guidelines for treatment and assessment of all areas affected by the condition.

Proprioception

The expression "Proprioception" refers to all neural inputs originating from joints, muscles, tendons, and associated deep tissue receptors [5]. It is not, as often referred to [6], a narrowly defined single sensory input that originates from one type of receptor with one function only. Rather, proprioceptive information must be understood as a group of sensation that is needed to accurately detect position and movement of joints, force and heaviness of external perturbations, coordination of motor commands and orientation of the body and its segments [7].

Table 1.1: International classification of functioning for chronic non-specific low back pain (adopted from [4])

ICF category	ICF code	ICF description
Body functions	b28013	Pain in back
	b28015	Pain in lower limb
	b7601	Control of complex voluntary movements
Body structure	s7601	Muscles of trunk
	s7602	Ligaments and fasciae of trunk
	s7402	Muscles of pelvic region
	s75001	Hip joint
	s75002	Muscles of thigh
	s75003	Ligaments and fascia of thigh
Activities and participation	d4106	Shifting the body's centre of gravity
	d4158	Maintaining a body position, specified as maintaining alignment of the trunk, pelvis and lower extremities such that the lumbar vertebral segments function in a neutral, or mid-range, position
	d4153	Maintaining a sitting position
	d4108	Bending
	d4302	Carrying in the arm
	d4303	Carrying on shoulders, hip and back
	d5701	Managing diet and fitness
	d2303	Completing the daily routine
	d6402	Cleaning living area
	d6601	Assisting others in movement
	d9202	Arts and culture
	e1151	Assistive products and technology for personal use in daily living
	e1351	Assistive products and technology for employment
	e1401	Assistive products and technology for culture, recreation, and sport

Postural control

According to Maki et al. [8], postural control can be defined as "the process by which the central nervous system (CNS) generates the pattern of muscle activity required to regulate the relationship between the center of mass and the base of support". This encompasses control of all body segments in order to counter any external perturbations and maintain a desired body position [9]. Healthy postural control requires the synergistic activation of muscle groups that prevent excessive sway outside the physiological range but allow enough flexibility to adapt to a dynamic environment [10].

Sensorimotor training

Movement of any segment is produced by muscle activity which in turn is commanded by cortical and sub-cortical nervous system responses to various stimuli [11]. The expression has been coined by a particular set of exercises that involve methods aimed at increased proprioceptive, vestibular, and optical afferent information processing and improved motor responses in dynamic environments. SMT emphasises postural control to progressively challenge synergistic stabilisation of load-bearing joints, in particular the spinal column [13, 10] and is expected to lead to improved quality of postural control.

Practically, the patients are instructed to use simple rehabilitation tools such as balance boards, elastic bands or a narrowed base of support to stand on. Beginning with simple static exercises, patients then progress through dynamic (e.g. with additional external perturbations) and functional (stepping or walking) exercises [6, 10]. There have been other terms used within the field of musculoskeletal rehabilitation, such as neuromuscular [14] or proprioceptive [15], but essentially all share the same goal: increased joint stability to alleviate pain and improve function.

Some basic principles have been described by Rasev [10] or Kim et al.[16], which should be adhered if any training effect is to be expected [16, 12, 17, 18]. First, the level of instability must be adjustable and incremental over time. The participant must be able to control the task to complete the exercise properly, but still be challenged when progressing his or her skills [10, 16]. Second, the participant must be able to respond to the instability, i.e. there must be a closed-loop control system in which feedback is compared to an intended goal [10, 16]. Finally, the exercise at hand must include a secondary task (i.e. dual task) which is separated from the functional stability task (e.g. juggling a ball or cognitive challenge) once the participant has advanced to a certain level in order to centralise the acquired skills [16].

Background

After introducing the terminology above, this section shall outline the interdependent relationship of pain, postural control, proprioception and sensorimotor training (Figure 1.1). A plethora

of research has been conducted in this area and it would go beyond the scope of this thesis to describe all of these findings. But the underlying theory and rationale for sensorimotor training in musculoskeletal rehabilitation should be understood in order to appreciate the investigated research questions of the following chapters.

Epidemiology of chronic non-specific low back pain

A recently published WHO report lists LBP as an explicit priority for the strategic agenda of health research (Priority Medicines for Europe and the World). According to their report [1], the lifetime prevalence of non-specific LBP is estimated at 60-70% in industrialised countries with a one-year prevalence of 15-45% (adult incidence 5% per year). Current guidelines report that up to 85% of individuals presenting for primary care with LBP have non-specific causes [19]. A cohort study from 2009 found that 42% of all participants presenting with acute LBP go on to develop CNLBP, in 11-12% to a limiting degree in terms of daily activities [20, 3]. CNLBP continues to be the leading cause of years lived with disability and is among the top ten conditions responsible for disability-adjusted life years. Through direct costs caused by treatments and indirect costs caused primarily by work absenteeism, this substantially weighs down on health care delivery systems and society [21]. Considering the high socio-economic burden caused by the condition, it remains important to monitor the efficacy of interventions [22, 23].

Suggested aetiology of chronic non-specific low back pain

CNLBP has always been, and still is, a challenging field for therapists and researchers alike, as self-reported pain cannot be objectively assessed through traditional methods such as imaging or functional assessments [24]. Yet, *"the pain is real, in that patients can feel it, despite what often cannot be found"* [23]. It takes a multidisciplinary approach to adequately assess and treat such a condition and therapists often find themselves confronted with not only musculoskeletal but also neurological features, psychological models and social aspects of the patient's life.

Whether the principle stress inflicted to the musculoskeletal system of these patients is of mechanical nature [25], purely attributable to centralised sensitisation with psychological excitation [26] or a combination of both [27] has been disputed for many years producing conflicting evidence with only meagre benefits for patients. Whereas the idea of centralisation is commonly approached with behaviour and educational therapy [26], a popular approach in physical and exercise therapy is to train core stability or learning how to stabilise certain regions during specific movements [28, 29]. However, considering the variability of human movement, it has been pointed out that motor control relies on several muscle synergies rather than one set of muscle chain required for stability [30]. For example, Rasev [10] claims that, in many cases, pain is the result of a postural dysfunction caused by decreased vestibular and proprioceptive afferent signalling. Inactivity, monotonous movement patterns, or long- term static posture that

impairs muscular coordination of the trunk and other weight bearing joints (e.g. cervical spine or pelvic joints) lead to corrupted afferent signalling [31]. It has been shown that patients with CNLBP have reduced precision control due to impaired proprioceptive signalling [32]. Reduced proprioceptive acuity could also be a results of CLNBP through the effects of nociceptive afference on muscle spindle feedback and reorganised primary somatosensory cortex [32]. Addressing the issue of causality, a series of studies have shown reduced adaptability of postural control strategies in young LBP patients. After demonstrating postural abnormalities in young LBP patients in a cross-section experimental condition with sensory manipulation and muscle fatigue [33], a longitudinal 2-year follow-up study found that symptom-free participants with similar strategies were at greater risk to develop CNLBP [34]. Only recently Pijnenburg et al. [35] found reorganisations of specific sensorimotor areas associated with the performance of dynamic postural control task using resting-state functional imaging methods. These findings are consistent with earlier theories by Janda [6], who claims that people with coordination difficulties are more likely to develop pain at a later stage in life [11]. Paraspinal muscle spindles and Golgi tendons have been shown to be part of sensory monitoring system that controls the spinal muscles and provides proprioceptive feedback to the sensory cortex [40]. Corrupted signalling through lesions in this region, intramuscular hernatoma and increased intracompartmental pressure, may impair sensory integrity and lead to prolonged muscle activation related to pain [41, 42, 43]. The subsequent imbalanced activation of local stabilising muscles, also termed functional joint instability, may cause painful overloading of muscles and passive joint structures [44]. If not restored, this constant malfunctioning of neuromuscular control may lead to inappropriate muscular activity [39, 45] and is thought to contribute to chronicity in CNLBP through CNS sensitisation [46]. However, the existence of actual proprioceptive deficits in patients with CNLBP has not been confirmed [36]. Based on these findings, models have been presented that suggest deficits in motor control lead to poor control of joint movement, repeated sub-lesions and pain [44, 47] (Figure 1.2)

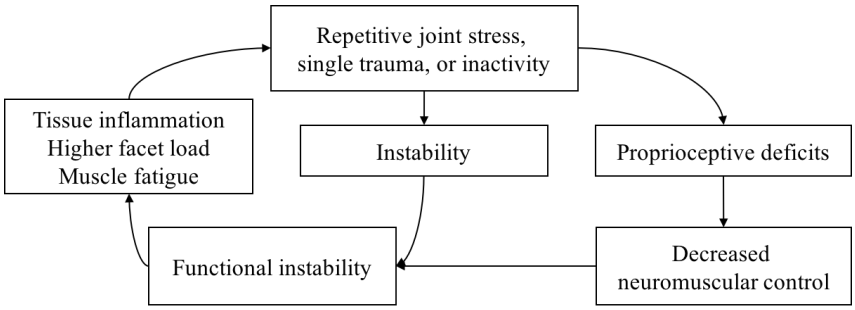

Figure 1.2: Theory-based mechanism of reduced functional joint stability and chronic low back pain (adapted from [47])

In order to diagnose functional joint instability, a simple provocation test of postural control has been suggested by Rasev et al. [10], where the subject is instructed to step three times on

a swaying platform and maintain stability standing on one leg. Poor postural control would be reflected in an increase of total platform sway recorded by means of an accelerometer, similar to centre of pressure (CP) displacement on a pressure sensitive plate. Assuming that postural control cannot be assessed by a summary outcome such as CP, the therapist must then evaluate the multi-segmental coordination of all joints, within just a few seconds. This is a challenge even to an experienced therapists. Multi-segmental and nonlinear kinematic assessments may prove valuable for such situations and are discussed in the next section.

Nonlinear assessment of postural control

In many ways, our behaviour, and particularly our posture, reveal how we feel, mentally as well as physically [48]. This observation gives rise to the possibility that certain systemic conditions could be detected through analyses of movement aberrations [49]. Dysfunction in any component of the sensorimotor system is reflected in some form of decreased quality of movement [11]. A long-standing belief in the assessment of postural control of people with LBP is that they perform poorly in single-leg stance and in postural control tests when compared with pain-free controls [50]. However, a recent systematic review, which accounts for methodological heterogeneity, concludes that this assumption may be flawed [51]. More specifically, the expected group differences are only apparent when sensory disturbance is applied, e.g. through muscle vibration [51].

Let us take a closer look at how postural control is actually regulated. With 792 muscles in the human body acting on more than one hundred joints [52], the human movement apparatus is a highly complex system. Harbourne et al. [53] wonderfully describes the underlying principles of complex biological systems. Complexity, in this sense, is defined as "highly variable fluctuations in physiological processes resembling mathematical chaos"[53]. Such systems are characterised by redundancy which allows them to follow a relatively predictable course but at the same time adapt to unpredicted changes in the environment [53]. Loss of complexity through loss of redundancy leads to loss of adaptability [53]. To assess complexity, measures based on mean magnitude alone are not sufficient. Nonlinear measures, on the other hand, allow description of the structure within time series which in turn reflects adaptability. It is important to introduce the concept of stability in human movement, as the term is applied for conflicting purposes [55]. Generally, stability describes a behavioural steady state of a system that will spontaneously return to this steady state after is has been perturbed [55]. In human movement, the pattern of coordination may change during which the system is unstable and attracted towards the preferred behavioural state [52]. This is achieved through specific muscle synergies acting cooperatively with joints and their passive elements (ligaments, sinews). This requires intrinsic and developed coordinative structures that have a natural tendency of inter-limb coordination patterns adopted with motor developments since early in life [52]. This is illustrated through the interaction of perception of a specific object and the specific movement preceding a reach-

and-grasp action [52]. This perception relies greatly on kinematic and kinetic feedback provided by proprioceptors to the CNS to influence accuracy of the movement and timing of the onset of motor commands. It has been shown that deafferented patients (only limited proprioceptive feedback) have more difficulties to adapt to movements that require non-preferred coordination patterns than healthy participants [56]. According to this Dynamic Pattern Theory, a specific stable pattern of behaviour results from certain conditions characterising the situation rather than from specific control mechanism that organise the behaviour (as opposed to the Motor Program Theory).

The Dynamic Pattern Theory is particular interesting to describe postural control and anticipated postural reactions. It has been argued that there are only two strategies for postural reaction the CNS can chose from: either hip, or ankle movement [57]. However, other joint segments have been shown to be as important as ankle and hip joints to stabilise the centre of mass (CM). The contribution of a variety of body segments allows compensatory mechanisms for postural flexibility and adaptability. This movement variability is an essential feature of motor control to perform efficiently in a variety of dynamic environments [54]. The relatively fixed patterns of muscle activations observed in early postural control assessments (i.e. hip-, or ankle-strategy) are likely to be two endpoints of a continuum of stabilising joint configurations. Results of more recent studies in healthy participants suggest that postural responses are organised in a flexible manner, specific to the task, that considers all degrees of freedom rather than pre-programmed sets of motor commands [58].

We used the uncontrolled manifold (UCM) index (UI) as the order parameter (functionally specific variable that defines the overall behaviour of a system) and the acceleration of the platform as control parameter to observe whether the order parameter remains stable or changes its stable state [58]. The UCM approach relates the segmental joint configurations to a single goal dependent variable to explain variability within the segment during a motor task. It has repeatedly been shown that healthy young adults have a natural tendency to return to their steady state after perturbation to their base of support [58, 59]. In these experiments, variance of the joint configuration which supports the stable position of the CM was significantly greater than the variance inducing CM deviation. These observations have led to the conclusion that the CM is an important variable of the postural system. We speak of an UCM-effect when the variability of the joint configurations which result in a stable value of a CM is significantly larger than the variability perpendicular to it. In later chapters of this thesis, where UCM will be presented as a outcome parameter, the term motor equivalence was used to describe the ability to use joint variability to stabilise the CM. The analysis is presented in more detail in the respective chapters (Chapter 4 and Chapter 5). But the basic principle applied was to analyse the variance of the difference of joint configurations before and following a platform perturbation. The post-perturbation naturally differs from the pre-perturbation configuration, but the extent to which the variance will be motor equivalent, may differ between individuals. The difference in joint configuration can be analytically projected onto the manifold of joint configurations that

allow motor equivalence and onto its orthogonal space, which represent non-motor equivalence (i.e. causes CM deviation).

Bearing in mind the list of observed motor control impairments in patients with CNLBP, the UCM would provide an interesting angle on the view of hypothesised reduced adaptability and inefficient muscular coordination patterns. Increased stiffness and spinal column rigidity [60] would reduce the amount of motor equivalent variance while lumbar hyper-mobility [44] may increase the amount of non-motor equivalent variance. Comprehensive assessment of dynamic postural control and improved postural reactions could be beneficial for patients with CNLBP if mechanical stimulus of pain can be removed and pain-related afferent sensory input may be altered [23].

Current guidelines and recommended interventions

The most recent European guideline for the management of CNLBP [3] favours limited rest, promotes resumption of daily activities even with minor pain and suggests that intensive multidisciplinary biopsychosocial rehabilitation with a functional restoration approach reduces pain and improves function in patients with chronic LBP [3]. The latter approach focuses on pain management rather than the pathological mechanism. Strong emphasis is put on the combination of manual, exercise and psychological treatments [61]. Only recently these recommendations were further substantiated by a large-scale randomised controlled trial that found higher rates of clinical relevant improvement in patient who attended mindfulness self-awareness classes combined with Yoga [62]. In contrast to this, current research findings do not support passive therapeutic movement or spinal manipulative therapy regarding long-lasting improvement of patients with CNLBP. Short-term effects observed in studies on passive hands-on treatments have been linked to nonspecific effects and are thought to enforce patient's pain belief rather than eliminate them[23]. Despite extensive research activity on the topic of CNLBP, which has significantly contributed to the understanding of pain [63], the European guidelines on the management of CNLBP conclude that the effects of specific exercises, such as SMT, must be further evaluated [3].

Role of sensorimotor training in low back pain treatment

Deemed as a functional approach, postural dysfunction theory acknowledges that local pain cannot be treated locally and should rather aim at improved self-regulation of joint-configuration through training methods that increase afferent and vestibular signalling rates. This is said to decrease local stress on ligaments and muscles, to reduce muscle imbalance and, ultimately, alleviate pain. There is theoretical reason to belief that SMT may have the potential to improve postural control and multi-segmental coordination. Within the postural dysfunction model explained above (Figure 1.2), this could be a potential treatment method in an attempt to alleviate pain and improve function.

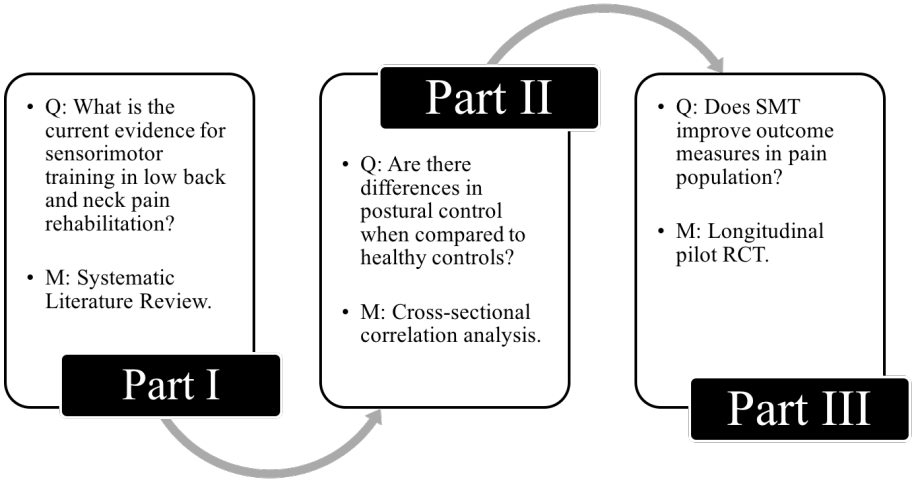

Figure 1.3: Overview of studies conducted for this dissertation

The theory behind SMT is, that using unstable support surface would elicit neuromuscular response with increased firing rates, to a greater extent than usual exercise (e.g. isolated strengthening exercise). Granacher et al. investigated effects of SMT in elderly men finding significant improvement in the SMT group for various postural outcomes [64]. However, with no active control group it cannot be specifically attributed to the SMT intervention. Whether SMT is a necessary adjunct to a ground-based exercises is still debatable and needs comprehensive review and evaluation.

In a guidance for prescribing exercise published by the American College of Sports Medicine [14], it had to be concluded that no definitive recommendations regarding quality and quantity can be given. Due to only scarce and variable data on the topic, no conclusive evidence for the benefits of SMT in young adults could be summarised [14]. Similarly, a Cochrane systematic review suggests there is no evidence for the efficacy of SMT for prevention of hamstring injury [65]. In a more dismissive tone, the promising effects of SMT for injury prevention and rehabilitation have been strongly contested by other researchers claiming that proprioception is often falsely labeled and misleading recommendations for treatments are given [12, 17].

Aims of the thesis

Neither postural control nor the effectiveness of SMT have been assessed adequately to date. The scientific evidence is still poor and contradicting. Thus, to step into this void and evaluate the true potential and limitations of SMT, this projects had two main objectives: (A) Propose an assessment that allows identification of dynamic multi-segmental deficiencies in patients suffering from chronic musculoskeletal pain and (B) to evaluate SMT as a therapeutic intervention to improve postural control and alleviate pain.

To achieve this, the project was divided into three parts (Figure 1.3). In Part I, a systematic

review of the existing literature on SMT in low-back pain rehabilitation was conducted (chapter 2). Part II, first consisted of the planning of a long-term study and publishing its study protocol (chapter 3). The therein proposed postural control parameters were then assessed in a cross-sectionally comparison of patients with CNLBP versus a healthy control group (chapter 4). Finally, in Part III, the effectiveness of SMT was compared with sub-effective low-intensity endurance (SLIT) training in patients with CNLBP on appropriate outcomes (pain, function, and motor control). Figure 1.3 provides an overview of the three parts and their aims.

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CHAPTER 2

Effects of proprioceptive exercises on pain and function in chronic neck- and low back pain rehabilitation: a systematic literature review

This chapter is based on [1]:

McCaskey, M. A., Schuster-Amft, C., Wirth, B., Suica, Z., & de Bruin, E. D. (2014). Effects of proprioceptive exercises on pain and function in chronic neck- and low back pain rehabilitation: a systematic literature review. BMC Musculoskeletal Disorders, 15(1), 382-17. http://doi.org/10.1186/1471-2474-15-382

[1] Figures, tables and language errors in the original publications were corrected for this thesis.

Abstract

Background: Proprioceptive training (PrT) is popularly applied as preventive or rehabilitative exercise method in various sports and rehabilitation settings. Its effect on pain and function is only poorly evaluated. The aim of this systematic review was to summarise and analyse the existing data on the effects of PrT on pain alleviation and functional restoration in patients with chronic ($\geq$3 months) neck- or back pain.

Methods: Relevant electronic databases were searched from their respective inception to February 2014. Randomised controlled trials comparing PrT with conventional therapies or inactive controls in patients with neck- or low back pain were included. Two review authors independently screened articles and assessed risk of bias (RoB). Data extraction was performed by the first author and crosschecked by a second author. Quality of findings was assessed and rated according to GRADE guidelines. Pain and functional status outcomes were extracted and synthesised qualitatively and quantitatively.

Results: In total, 18 studies involving 1380 subjects described interventions related to PrT (years 1994 − 2013). 6 studies focussed on neck-, 12 on low back pain. Three main directions of PrT were identified: Discriminatory perceptive exercises with somatosensory stimuli to the back (pPrT, $n = 2$), multimodal exercises on labile surfaces (mPrT, n = 13), or joint repositioning exercise with head-eye coordination (rPrT, $n = 3$). Comparators entailed usual care, home based training, educational therapy, strengthening, stretching and endurance training, or inactive controls. Quality of studies was low and RoB was deemed moderate to high with a high prevalence of unclear sequence generation and group allocation ($> 60\%$). Low quality evidence suggests PrT may be more effective than not intervening at all. Low quality evidence suggests that PrT is no more effective than conventional physiotherapy. Low quality evidence suggests PrT is inferior to educational and behavioural approaches.

Conclusions: There are few relevant good quality studies on proprioceptive exercises. A descriptive summary of the evidence suggests that there is no consistent benefit in adding PrT to neck- and low back pain rehabilitation and functional restoration.

Background

Treatment of chronic pain has always been, and still is, a challenging field for therapists and researchers alike. Treatment is particularly problematic in patients who report significant pain with associated limitations for daily activities, but present with no structural or organic causes. More than 80% of all chronic low back pain (LBP) patients referred to physiotherapy are diagnosed with such non- specific LBP (CNLBP) causing corresponding figures in medical costs [1]. Despite the progress in the understanding of pain and its management, CNLBP is still stated as the leading cause for years lived with disability, worldwide [2]. With the expected increase of this global burden over the next decades [3] there is still an urgent need for effective CNLBP treatment.

According to a recent, integrative model of chronic CNLBP development, changes in the amount and pattern of movements is at the beginning of pain chronification processes [4]. Flawed movements caused by either fear in response to an acute pain episode or environmental conditions (e.g. repetitive movements at work, or sustained postural misalignment) are believed to lead to impaired sensorimotor control and have been suggested to contribute to tissue pathology in CNLBP [4, 5, 6, 7, 8, 9, 10]. The relationship of pain and changes in motor control has been shown in several studies [11, 12, 13, 14, 15, 16, 17] and is seen as a protective reaction of the body to limit provocation of the painful area [9]. This, in the long run, can cause further damage, exacerbate the symptoms through peripheral and central nervous system sensitization (lowering of pain threshold), and promote dysfunctional movement patterns [4, 10, 18]. A commonly described theory suggests that reduced afferent variability from peripheral proprioceptive receptors may cause neuromuscular deficiencies. If not restored, this constant malfunctioning of neuromuscular control and flawed regulation of dynamic movements may lead to inappropriate muscular activity (i.e. overor under-utilization) [19, 20, 21, 22]. This is thought to contribute to taut muscles, imbalanced muscle activation, poor posture, and ultimately to musculoskeletal pain in lumbar regions [4, 10, 19, 20, 21, 23]. Psychosocial factors can contribute to decreased physical activity and enforce the 'vicious cycle' described above [4].

This 'functional pathology' theory [10] is supported by several findings in current literature. It has been shown that patients with CNLBP have modified muscle recruitment patterns [4, 24, 25, 26], reduced postural robustness [6], inappropriate variability in postural control [27, 28, 29, 30] and seem to rely more on distal proprioception [6] due to impaired proprioception from proximal segments [6, 31]. Such deficits in the motor system occur early in the history of onset of pain [32] and have been associated with a decreased ability of the central nervous system to process proprioceptive inputs [33].

Proprioception is defined as afferent information that contributes to conscious muscle sense, total posture, and segmental posture [34]. Proprioceptive feedback influences movement accuracy, timing of the onset of motor commands, and adapting to movement situations that require the use of non-preferred coordination patterns [35]. Maintaining proprioceptive integration in

neuromuscular control of posture has been identified as important resource for unimpaired and pain-free participation of daily activities [36]. Furthermore, improvement of neuromuscular function of the trunk has been suggested to be more important than strengthening in patients with LBP [15, 26, 37]. Consequently, neuromuscular rehabilitation techniques addressing sensory deficiencies through increased proprioceptive challenge have emerged in recent years and have received increasing therapeutic attention [22, 23, 38].

Restitution of healthy neuromuscular motor patterns and increased sensory input variation is thought to reduce mechanical stress through improved muscular coordination and may prevent recurrence of CNLBP [32, 39]. So far only poorly evaluated, potential benefits are expected from proprioceptive exercises and joint position training to reduce pain and disability [40]. These exercises would generally entail balance training and the use of labile platforms to repeatedly provoke sensory receptors and subsequent integration of these perceptions in the spinal cord, pons, and higher cortical areas [41, 42]. This is thought to lead to increased perception of joint position and motion, hence supporting unconscious joint stabilisation through reflex which again maintains healthy posture and balance [23].

There is an increasing amount of used expressions and a wide variability in the nature, mode and context of methods attempting similar effects. Moreover, there has been some doubt on whether PrT can improve proprioceptive acuity in a functional way at all. In a recent narrative review, Ashton-Miller et al. outlined a row of concerns (e.g. lack of neurophysiological evidence) about the validity of current proprioceptive exercises [43]. Although many therapists and clinicians report successful treatment cases, the exact effect and validity of sensorimotor interventions is still discussed controversially [43, 44]. Accordingly, European Guidelines on the management of chronic nonspecific LBP do not include recommendations for PrT [45]. However, maintaining variability of the collective sensory input is the basis of the dynamics behind human movement, allowing adjustable functional behaviour [46]. Although it remains unclear whether reduced proprioception is the cause [5] or the result of musculoskeletal pain [47, 48], improvement of pain has been linked to changes in neural activation [49] and psychological changes [50].

This article systematically reviews sensorimotor training procedures that target maladaptive changes in patients suffering from chronic non-specific neck- or low back pain. The main objective is to investigate current evidence supporting the effectiveness of integrated sensorimotor training concepts with proprioceptive elements in musculoskeletal pain rehabilitation that aim at reducing pain and improving functional status. Furthermore, studies reporting positive outcomes (improvement of functional status and reduced pain) shall be identified to describe what practical features of sensorimotor training are necessary to be successful and effective.

Methods

Only randomised controlled trials were included for this systematic review (SR). Titles retrieved from electronic search, were screened by two authors (MM and CS). To qualify as an eligi-

ble study, participants had to be of adult age (>18 years), present with chronic non-specific musculoskeletal neck- or low back pain (at least three months), including whiplash-associated disorders. Only studies declaring clinical examination or interview assessment of pain were included. Exclusion criteria were neurological deficits related to peripheral or central nerve damage, vestibular diseases, osteoarticular diseases (e.g. rheumatoid arthritis), fractures, and tumours. No restrictions regarding gender, ethnicity, language, or clinical setting (in-patients or out-patients) were made. Pain during or after pregnancy, complex regional pain syndrome, headache alone, and fibromyalgia were also added to the exclusion criteria.

The effectiveness of PrT was compared to other forms of exercise, educational interventions, and to inactive control groups. All variations of PrT, where active participation of the patient was described (balancing- and perturbation exercises, joint repositioning) were included. Passive methods, where patients did not actively have to respond to peripheral feedback (e.g. exercises on vibrating platforms), were excluded. Also Yoga, Pilates, and Global Postural Re-education (GPR) were not included. The search was not limited to one kind of comparator. All forms of control-interventions were included (e.g. massage or educational, strengthening exercises, endurance training, etc.). The a-priori defined research question and protocol is provided as Additional file 1 (see online publication). An overview of the eligibility criteria of included studies can be found in the Additional file 2 (see online publication).

Information sources and search strategy

The Cochrane Central Register of Controlled Trials CENTRAL (The Cochrane Library 2014, Issue 2) and further databases were searched from their respective inception to February 2014 (MEDLINE via Ovid, EMBASE, CINAHL via EBSCOhost, SportDISCUS, and SCOPUS). Medline and SCOPUS were combined in order to cover the gaps in citations published prior to 1996. Reference lists of included articles were reviewed for further citations. A combination of medical subject headings (MeSH: Musculoskeletal Pain, Low Back Pain, Fibromyalgia, Reflex Sympathetic Dystrophy, Joint Instability, Shoulder Pain, Myofascial Pain Syndromes) and search terms (pain, discomfort, trouble, hurt, muscle imbalance, muscle stiffness, shoulder-, neck-, pelvic- or back pain) was used for the population. For the intervention, the following search terms were combined: sensory motor or sensorimotor, proprioceptive, balance, postural, coordination, motor control, cybernetic, stabilising. The search was not restricted to specific outcomes. The first search was executed on December 6th 2012 by a Life Science librarian from a medical library and, as an update of the search, repeated with saved searches on February 25th 2014 (Figure 2.1). An example search is provided as Additional file 3 (see online publication).

Study selection

De-duplication had been performed by the assigned librarian when two review authors (MM & CS) independently screened articles for inclusion criteria according to standardised protocol.

Titles, abstracts, and full texts were screened sequentially. Disagreement of selected full texts was resolved with mutual consent. If authors could not agree upon the issue, the last author (EdB) was consulted to decide on in- or exclusion. Foreign language full texts were not excluded immediately. Instead, the authors or institutions were contacted to elucidate whether a translated version of the article was available. With no English or German version available, the reference was excluded.

Data collection process

One review author (MM) extracted all data and recorded it on a standardised data-extraction form based on the template by the Cochrane Pain, Palliative & Supportive Review Group [51]. The data extraction form was pilot- tested on four studies, and refined accordingly. A second review author (CS) crosschecked the extracted data on three randomly selected studies (randomised with random number generator on Microsoft Excel). Disagreements were resolved by discussion between the two review authors; if no agreement could be reached, it was planned a third author (EdB) would decide. Inter-rater agreement above 90% was deemed satisfactory. The extracted data included study design and methodology (including randomisation procedures and settings), participants' characteristics, details of the interventions, dropouts and withdrawals, and outcome measure's change from baseline to endpoint. In case of inconclusive data (e.g. only graphical presentation, missing variance of change), the original authors or institutions were contacted to obtain missing details.

Risk of bias in individual studies

As the Cochrane Collaboration discourages the use of summary scores for RoB assessment, two reviewers (MM & CS) independently applied the Cochrane Collaborations tool to judge the risk of over or underestimating the effects of an intervention [52]. In total, twelve domains of bias were rated for every study, each domain having three rating categories (Figure 2.2): (1) low RoB, (2), high RoB and (3) unclear RoB. Rating (1) is unlikely to alter the results significantly, (2) seriously weakens confidence in the results, and (3) raises some doubt about the results. With insufficient information on an item the score given was "unclear". As suggested by the Cochrane Back Review Group (CBRG) [53], more topicspecific sources of biases were assessed. Specifically, baseline similarity, equal dose and frequency of co-interventions, compliance, adherence to intention-to-treat analysis, and timing of outcome assessment were compared between the groups. The arbitration of a third reviewer (EdB) was used in the event of any disagreement between the reviewers (MM & CS) for both ratings. Percentage agreement and Cohen's kappa were calculated and interpreted in accordance with Landis and Koch's benchmarks for assessing the agreement between raters: poor (0), slight (0.0 to 0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), substantial (0.61 to 0.80), and almost perfect (0.81 to 1.0) [54].

Analysis and GRADE approach

The review topic includes a wide range of intervention methods (different concepts of sensorimotor training) and participants (non-specific musculoskeletal back- or neck- pain). The collected data is therefore prone to high heterogeneity, which discourages a meta-analysis. To test for statistical heterogeneity, data was entered into Review Manager (RevMan5, The Cochrane Collaboration, Oxford, UK) and Microsoft Excel (2010) to calculate mean differences (MD), standard deviation (SD), confidence intervals (CI), and p-values (p). Missing SDs and MDs were calculated according to the Cochrane Handbook for Systematic Reviews [55], if applicable. Funnel plots of the trial's SMD were evaluated using Review Manager (RevMan5, The Cochrane Collaboration, Oxford, UK). Asymmetry in a funnel plot indicates possible non-publication of small trials with negative results [55]. Interventions were compared based on clinical homogeneity (study population, types of treatment, outcomes and measurement instruments) and choice of proprioceptive training modality. Trials that used the same tools for outcome assessment were compared using the mean difference (MD) to allow direct comparison of the results. If trials within the same comparison used different measurement tools for the same outcome, the standardized mean difference (SMD) was calculated using random-effect models. If only graphs were available, the mean scores and standard deviations (SD) had to be estimated from the illustrations. If missing SDs of change were not available, SDs of post-treatment scores were used [55]. If SDs for outcomes were not reported at all, they were estimated using the mean SD weighted by the relevant treatment group's sample size across all other trials that reported SDs for same outcome [53]. The GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach was used to rate the overall quality of the evidence and the strength of the recommendations [53]. Following the CBRG method guidelines [53], five domains of quality were rated for each comparison: (1) Limitations of study design ($>$ 25% of participants from studies with high risk of bias); (2) Inconsistency (i.e. opposite direction of effects and/or significant statistical heterogeneity); (3) Indirectness (e.g. only one gender or specific age group included); (4) Imprecision (e.g. too few participants or only one study included); (5) Publication bias across all trials. Rating was conducted by one author (MM) and crosschecked by a second (ZS) on randomly selected comparisons. The four-point rating scale ranged from 'High quality' on one end to 'Very low quality' on the other end. To qualify as high quality evidence, more than 75% of the RCTs within a comparison had to be judged to have no limitations of study design, have consistent findings among multiple studies, present direct (generalizable) and precise data, without known or suspected publication bias. The quality of the summary of findings was rated as moderate if one, low if two, and very low if three of the criteria were not met. The definitions of quality of the evidence were adopted from Guyatt et al. [56]: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important

impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

Results

Study selection

After adjusting for duplicates, the latest search of the databases provided a total of 1929 citations. Of these, 1901 were discarded after reviewing titles and abstracts, clearly showing that these papers did not meet the criteria. Three additional studies were discarded because full texts of the study were not available or the papers could not be feasibly translated into English. The full texts of the remaining 25 citations were examined in more detail. Finally, 18 studies met the inclusion criteria and were included in the SR. No unpublished relevant studies were obtained (Figure 2.1).

Study characteristics

The included 18 studies, all describing interventions related to PrT, were published between 1994 and 2013, all of them in English. The reports describe randomised controlled trials with one to three comparators (Table 2.1). The studies involved a total number of $N = 1380$ subjects with clinically confirmed or self-reported chronic pain persisting for more than three months. Mean symptom duration also varied largely with a range from 8.7 to 328.2 months. The review included 6 studies focussing on neck pain ($N = 297$) and 12 on LBP ($N = 1069$). Sample size ranged from 14-207 ($mean\ N = 77 \pm 53$; $48\%\ females$, $mean\ age = 46 \pm 8 yrs.$). One study did not report age [57], two studies included women [58] or men [59] only. Most patients were outpatients to the institute carrying out the trial. In one study, the tests were conducted outside the institute at the patients' workplaces [59]. In most trials the investigator examined the patients for clinical diagnosis. In seven studies, self-report assessments, i.e. pain questionnaires were used for eligibility selection.

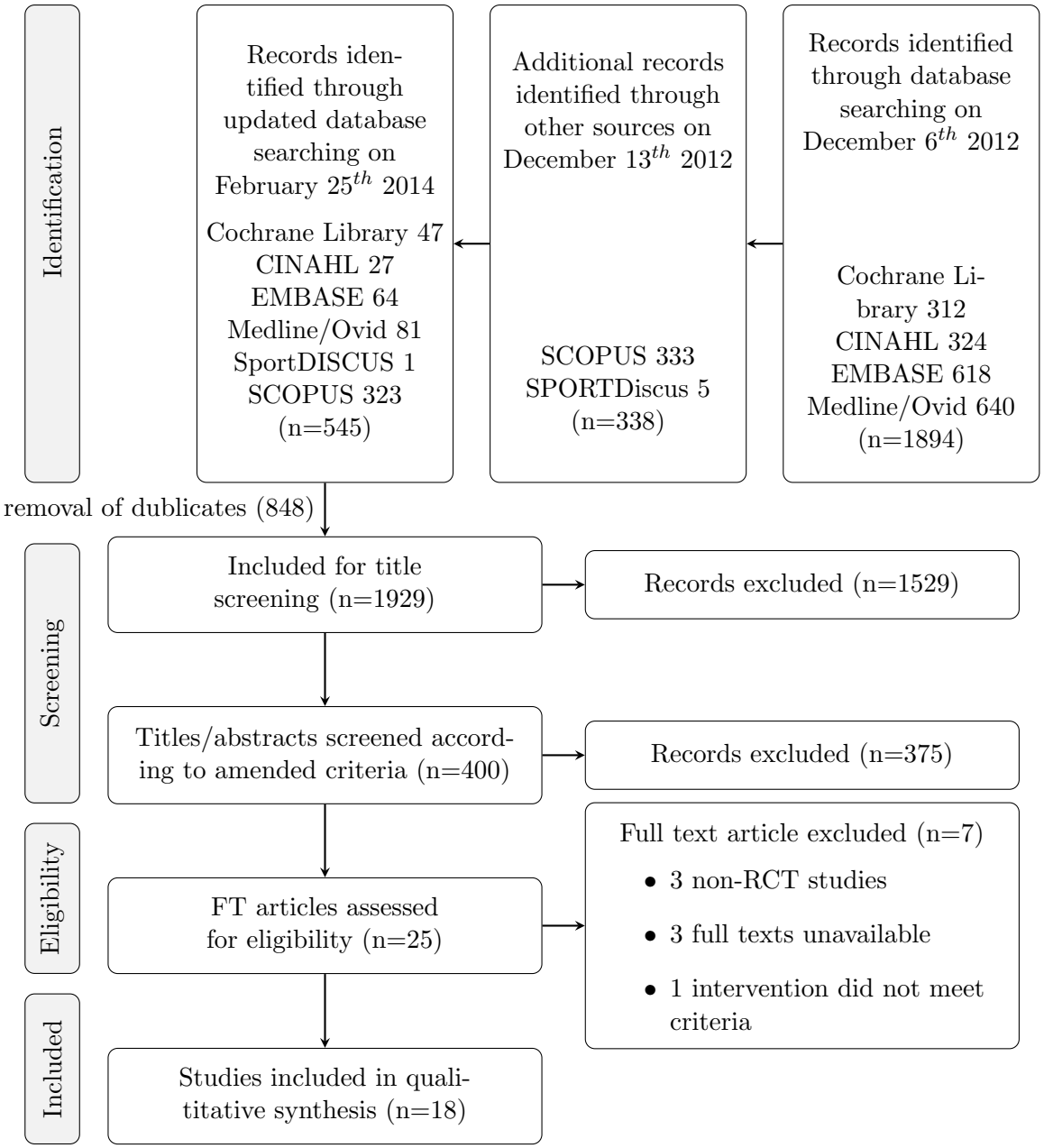

Figure 2.1: Screening progress flow chart (n=number of references; RCT=randomized controlled trials, FT=full-texts)

Table 2.1: Overview of included studies and descriptive study data

Reference	Participants		Intervention	Comparator	Outcome	Group effect
Beinert [60]	Total N:	34	5 weeks, 15x15 min., three	No intervention; participants	Numeric Pain Rating Scale (NRS)	↗
CH, 2013	Age:	23	balance exercises with	were instructed to maintain	Head relocation from neutral position	↗
	Pain area:	NP	increasing difficulty: single	physical activity as usual	Pre-rotated head relocation	↗
	Cl. confirmed:	No	leg, tandem, and standing on			
	Gender (f/m):	nA	a wobble board			
Chung [61]	Total N	24	8 weeks, 3 sessions/week	8 weeks, 3 sessions/week	Pain intensity VAS	=
KR, 2013	Age:	38	(duration not specified), 10	(duration not specified), 10	Oswestry Disability Index (ODI)	↗
	Pain area:	LBP	Min. warm-up followed by	Min. warm-up followed by	Weight bearing (postural sway)	=
	Cl. confirmed:	Yes	four lumbar stabilisation	four lumbar stabilisation	Multifidus cross section L2&L3	=
	Gender (f/m):	11/13	exercises on a small	exercises on a mat	Multifidus cross section L4&L5	↗
			gymnastics ball			
Costa [62]	Total N	154	8 weeks, 12x30 min. motor	8 weeks, 12x25 min.	Numeric Pain Rating Scale (NRS)	=
AU, 2011	Age:	54	control exercise to improve	Shortwave Diathermy,	Patient Specific Functional Scale (PSFS)	↗
	Pain area:	LBP	function of specific muscles of	Ultrasound (placebo)	Global Impression of Recovery (GPE)	↗
	Cl. confirmed:	No	the low back and control of		Roland Morris Score (RMS)	↗
	Gender (f/m):	28/51	posture and movement			
Frih [63]	Total N	107	4 weeks, 28x30 min.	4 weeks, 12x90 min. standard	Pain intensity VAS	↗
TN, 2004	Age:	36	home-based rehabilitation	rehabilitation programme:	MacRae Schber Index	=
	Pain area:	LBP	programme: postural control,	analgesic, electrotherapy, pain	Finger-to-Floor (FTF) distance	=
	Cl. confirmed:	Yes	stretching and strengthening	management, stretching,	Thigh-leg (TL) angle	=
	Gender (f/m):	80/25	exercises	proprioceptive, and	Shirado Test	↗
				strengthening exercises	Sorensen Test	=
					Quebec Functional Index	=
Gatti [64]	Total N	179	5 weeks, 10x60min. treadmill	5 weeks, 10x60 min. treadmill	Pain Intensity VAS (0 to 100)	=
IT, 2009	Age:	58	(15 min.), flexibility (30 min.),	(15 min.), flexibility (15 min.),	Roland Morris Score (RMS)	↗
	Pain area:	LBP	and trunk balance (15 min.)	and strengthening (15 min.)	Quality of Life, physical (SF-12p)	↗
	Cl. confirmed:	Yes	exercises	exercises	Quality of Life, mental (SF-12m)	=
	Gender (f/m):	11/23				

Table 2.1: Overview of included studies and descriptive study data *(continued)*

Hudson [65]	Total N	14	6 weeks, 6x40 min.	6 weeks, 5 to 8 usual care	Neck Disability Index (NDI)	=
UK, 2010	Age:	43	multimodal treatments:	treatments (any combination	Numerical Pain Rating Scale (NRS)	=
	Pain area:	NP	coordinative, proprioceptive,	of exercise, education,		
	Cl. confirmed:	No	strengthening, and	mobilisations, manipulations,		
	Gender (f/m):	8/4	educational components	electrotherapy, or		
				acupuncture)		
Humphreys [57]	Total N	63	4 weeks, 56 treatments (twice	No intervention	Head Repositioning HRA	↗
UK, 2002	Age:	nA	a day, duration not specified)		Self-reported Pain Intensity (VAS)	↗
	Pain area:	NP	coordinative exercises			
	Cl. confirmed:	No	(eye-head-neck coordination)			
	Gender (f/m):	nA				
Jin [66]	Total N	14	4 weeks, 20x40 Min. Six	4 weeks, 20x40 Min. physical	Pain intensity VAS	↗
KR, 2013	Age:	45	different quadruped exercises	therapy (20 Min. hot press; 5	Oswestry Disability Index (ODI)	↗
	Pain area:	LBP	on a wobble board	Min. ultrasound; 15 Min.	Anticipatory postural adjustment	↗
	Cl. confirmed:	No		transcutaneous electrical		
	Gender (f/m):	8/6		nerve stimulation)		
Johannsen [67]	Total N	40	12 weeks, 24x60min. warm up	12 weeks, 24x60min.	Isokinetic back strength (KinCom II)	=
DK, 1999	Age:	38	(10 min.) coordinative,	endurance (10 min.), dynamic	Patient's general assessment	=
	Pain area:	LBP	proprioceptive, balance, and	strengthening exercises (40	Pain score (0-8)	=
	Cl. confirmed:	Yes	stability exercises (40 min.),	min.), and stretching (10	Mobility score (cm)	=
	Gender (f/m):	93/120	stretching (10 min.)	min.)		
Jull [58]	Total N	64	6 weeks, 84x10 min. (twice	6 weeks, 84x10 min. (twice	Joint Position Error (JPE) Left	=
AU, 2005	Age:	41	per day) proprioceptive	per week) strengthening of	JPE Right	↘
	Pain area:	NP	training (head relocation	deep cervical flexor muscles	JPE Extension	=
	Cl. confirmed:	Yes	practice), coordinative		Neck Disability Index (NDI)	=
	Gender (f/m):	64/0	exercises (eye/head		Numerical Rating Scale (NRS)	=
			coordination)			

Table 2.1: Overview of included studies and descriptive study data *(continued)*

Marshall [68]	Total N	54	4 weeks usual care, then 12	4 weeks usual care, then 12	Oswestry Disability Index	=
NZ, 2008	Age:	35	weeks, 12 proprioceptive and	weeks home based therapy	FR-Response	=
	Pain area:	LBP	strengthening exercises using	regime based on commonly	Feed-forward activation assessmente	=
	Cl. confirmed:	No	the therapy ball (Swiss ball)	recommended low back		
	Gender (f/m):	27/27		strengthening exercises		
Morone [69]	Total N	75	4 weeks, 12x45 min.	3 weeks, 10 sessions (duration	Visual Analogue Scale	↗
IT, 2011	Age:	55	perceptive rehabilitation with	per session not reported),	McGill Pain Rating Index	↗
	Pain area:	LBP	proprioceptive components	Back School based on	Oswestry Disability Index	=
	Cl. confirmed:	Yes		re-education of breathing,	Wadell Disability Index	=
	Gender (f/m):	54/21		stretching, postural, and		
				strengthening exercises		
Morone [69]	Total N	75	4 weeks, 12x45 min.	No intervention	Visual Analogue Scale	↗
IT, 2011 [69]	Age:	55	perceptive rehabilitation with		McGill Pain Rating Index	↗
	Pain area:	LBP	proprioceptive components		Oswestry Disability Index	=
	Cl. confirmed:	Yes			Wadell Disability Index	=
	Gender (f/m):	54/21				
Paolucci [70]	Total N	45	4 weeks, 12x45 min.	3 weeks, 10 sessions (duration	McGill Pain Questionaire	=
IT, 2012	Age:	59	perceptive treatment with	per session not reported),	Centre of Pressure (CoP) area	nA
	Pain area:	LBP	proprioceptive components	Back School based on	CoP sway length	nA
	Cl. confirmed:	Yes		re-education of breathing,	CoP sway velocity AP	nA
	Gender (f/m):	nA		stretching, postural, and	CoP sway velocity LL	nA
				strengthening exercises		
Revel [71]	Total N	60	8 weeks, 16x45min.	Symptomatic analgesics	Head Repositioning Accuracy (HRA)	↗
FR, 1994	Age:	46.8	symptomatic analgesics,		Self-reported pain VAS	↗
	Pain area:	NP	proprioceptive (head		Active Range of Motion: Extension	=
	Cl. confirmed:	Yes	relocation practice), and		Active Range of Motion: Rotation	↗
	Gender (f/m):	51/10	coordinative (eye/head		NSAID intake	=
			coordination) exercises, and		Self-assessed functional improvement	↗
			coordinative exercises			

Table 2.1: Overview of included studies and descriptive study data *(continued)*

Sorensen [72]	Total N	207	3 to 9 weeks, 1 to 3 x 30 to 60	Undefined duration. Symptom	Numeric Pain Rating Scale (NRS)	=
DK, 2012	Age:	39.5	min. educational program,	based physical training	Activity Limitation Scale	=
	Pain area:	LBP	stretching	programme, motor control of	Fear Avoidance Beliefs Questionnaire	↘
	Cl. confirmed:	Yes		posture and movement OR	Back Beliefs Questionnaire	=
	Gender (f/m):	105/95		therapy ball and dynamic		
				exercises for balance,		
				endurance, and strength		
Suni [59]	Total N	106	48 weeks, 96 x 10 exercises for	No intervention (control	VAS (past 7 days)	=
FI, 2006	Age:	47.3	balance, coordination,	group)	ODI	=
	Pain area:	LBP	strength, stretching, motor		PDI	=
	Cl. confirmed:	Yes	control, and educational			
	Gender (f/m):	0/100				
Stankovic [73]	Total N	160	4 weeks, 20x30 min. motor	4 weeks, 20x30 min.	Oswestry Disability Index (ODI), overall	↗
RS, 2011	Age:	49.5	control, strengthening,	strengthening and stretching	ODI, subscale Pain	↗
	Pain area:	LBP	relaxation, breathing,	aerobic exercises		
	Cl. confirmed:	No	stretching, proprioceptive, and			
	Gender (f/m):	60/140	coordinative exercises			
Taimela [74]	Total N	76	12 weeks, 12x45min.	Neck lectures and activated	Cervical range of motion	=
FI, 1999	Age:	42.3	multimodal treatment: muscle	home exercises (home	Cervical pressure pain threshold	=
	Pain area:	NP	endurance and coordination,	exercises were introduced and	Pain intensity (100mm VAS)	=
	Cl. confirmed:	Yes	relaxation training,	explained in the first two	Fear Avoidance Beliefs Questionnaire	=
	Gender (f/m):	36/14	educational, motor control,	weeks)	Physical impairment in daily activities	=
			postural control			
Taimela [74]	Total N	76	12 weeks, 12x45min.	Neck lecture and	Cervical range of motion	=
FI, 1999	Age:	42.3	multimodal treatment: muscle	recommendation of exercises	Cervical pressure pain threshold	=
	Pain area:	NP	endurance and coordination,		Pain intensity (100mm VAS)	↗
	Cl. confirmed:	Yes	relaxation training,		Fear Avoidance Beliefs Questionnaire	=
	Gender (f/m):	36/14	educational, motor control,		Physical impairment in daily activities	=
			postural control			

LBP=low back pain; NP=neck pain; ↗ in favour of proprioceptive training (PrT); ↘ in favour of comparator; = no significant difference. Country codes: AU=Australia; CH=Switzerland; DK=Denmark; FI=Finland; FR=France; IT=Italy; KR=Republic of Korea; NZ= New Zealand; RS=Republic of Serbia; TN=Tunisia; UK=United Kingdom.

Interventions

Most interventions had patients exercising over a period of 4 to 8 weeks. One study followed patients for one year with measuring events at 6 months and 12 months [59]. Three major directions of PrT were identified. The interventions were described as (1) perceptive PrT (pPrT) where discriminatory perceptive exercises with somatosensory stimuli to the back and joint position sense is practiced [69, 70], (2) as multimodal PrT (mPrT) postural control or balance exercises on labile surfaces often combined with other forms of exercise [59, 65, 67, 72, 74, 63, 73, 62, 68, 60, 66, 61], or as (3) head relocation PrT (rPrT) with head-eye coordination exercise [57, 58, 71]. Comparators entailed usual care, home based training, educational therapy, or strengthening, stretching and endurance training. In one study, the intervention was placebo-controlled. The durations of the interventions were between four weeks and 52 weeks ($median = sixweeks$). Table 2.1 displays an overview of different modalities and dose descriptions.

Outcomes

Apart from numerical pain rating scales (NRS) and visual analogue scales (VAS), pain outcomes also included the pain subscale from the Oswestry Disability Index (ODI pain), or the McGill Pain Questionnaire; outcome measures on functional status included ODI, the Neck Disability Index (NDI), the Quebec questionnaire and the Roland Morris questionnaire (RMS). For both outcomes, several authors also used self-developed questionnaires (e.g. self-reported functional impairment on non-standardised scales [71]). Other outcomes assessed range of motion, joint repositioning accuracy, anticipated postural adjustment, and pressure plate posturography. These outcomes were, however, only measured in individual studies and not comparable to other studies within the SR. Furthermore, they were often non-standardised, hence not comparable to studies outside the SR either. For these reasons they were not further evaluated in this SR but included in the overview (Table 2.1).

Risk of bias within studies

Arbitration of the third reviewer (EdB) was required for several trials. However, overall inter-rater agreement was found to be substantial with $Kappa = 0.73$ ($p < 0.001$, $SE = 0.06$, $95\%CI : 0.62 - 0.84$). Only one trial was deemed free of RoB (Costa et al. [62]). The RoB assessments of all other studies raised some doubt about their results or suggested weakened confidence in the results (Figure 2.2). Most trials (72%) were rated with a low risk of bias in more than five items of the assessment tool. However, although all studies were registered as RCTs, only 4 trials (22%) clearly reported allocation concealment or use of adequate randomisation procedures. In three studies (17%) the description of blinding suggested high risk of detection bias, as assessor and clinicians appeared to be the same person. Due to study group imbalances at baseline (39%), high dropout rates (34%) and uncontrolled co-interventions (33%) were rated

to pose additional high or unclear RoB.

Risk of bias across studies

Analysis of funnel plots suggested low publication bias in both synthesis of pooled pain and function. See Additional file 4 to view the funnel plots.

Results of individual studies

Tables 2.2, 2.3, 2.4 illustrate the synthesised results based on the GRADE considerations described above.

Comparisons I: pPrT versus other exercises or inactivity

Two studies, one with a low risk of bias [69] the other with high risk of bias [70], compared pPrT with other exercises. In both studies, the exercise group also received back education as part of the control intervention (Table 2.2). Both studies evaluated pain intensity as an outcome, although only one recorded long-term follow- up results [69]. The pooled SMD (95% CI) between groups was -1.15 (-2.93 to 0.63) in the short-term. The follow-up results of the long-term RCT showed no significant difference between back school exercises and pPrT groups ($N = 45$). There is very low quality evidence that pPrT is more effective for pain reduction than back school exercise in the short-term (two RCTs; $N = 80$; limitations in design, imprecision, inconsistency). The RCT with low RoB [69] additionally compared pPrT to an inactive control group. The pain score was significantly lower in the pPrT group than in the inactive control group at the end of the treatment ($N = 50$) and at the long- term follow-up ($N = 45$). Study outcomes also included a back specific functional status, assessed with the Oswestry Disability Index. No significant group differences were found at short- ($N = 45$) or long-term follow-up ($N = 50$) for this outcome. With only one RCT and limitations in imprecision and indirectness (due to applicability of intervention and small total sample size) there is low quality evidence that there is no significant difference in effect on functional status between pPrT and not intervening at all. Further, there is only low quality evidence that pPrT is more effective for pain rehabilitation when compared to inactive controls.

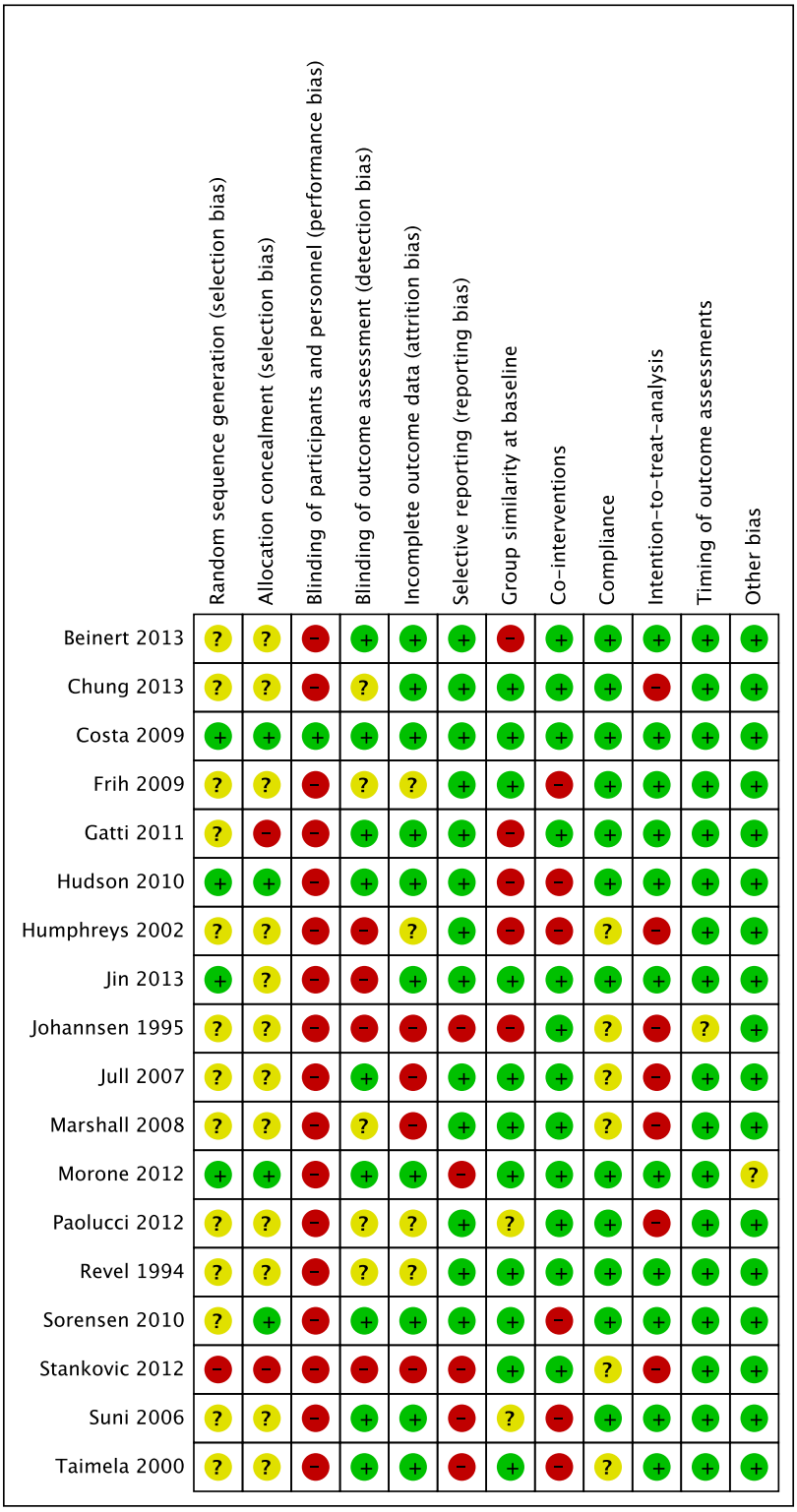

Figure 2.2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study. (+) = Low risk of bias; (-) = high risk of bias; (?) = unclear risk of bias.

Table 2.2: Summary of findings of comparison I (perceptual proprioceptive training versus inactive controls or other exercise)

Patient or population: adults with non-specific chronic low-back pain.
Settings: primary and secondary health care centres.

Outcomes	**Illustrative means (95% CI)**		**N (studies)**	**GRADE**	**Comments**
	Control group	**Intervention group**			
Comparison 1.1	**Inactive control**	**pPrT**			
Pain intensity VAS (0-10) short-term follow-up	The mean pain intensity of the control group was **7.32 points**.	The mean pain intensity in the intervention group was **3.16 points lower** (4.7 to 1.95 lower).	50 (1 study)	++00 low[2,3,§]	Significant
Pain intensity VAS (0-10) short-term follow-up	The mean pain intensity of the control group was **7.32 points.**	The mean pain intensity in the intervention group was **3.16 points lower** (4.7 to 1.95 lower).	50(1 study)	++00 low[2,3,§]	Significant
Pain intensity VAS (0-10) long-term follow-up	The mean pain intensity of the control group was **7.48 points**.	The mean pain intensity in the intervention group was **3.04 points lower** (4.38 to 1.70 lower).	45 (1 study)	++00 low[2,3]	Significant
Back specific functional status ODI short-term follow-up	The mean pain intensity of the control group was **24.32 points**.	The mean ODI score in the intervention group was **4.48 points lower** (11.83 lower to 2.87 higher).	50 (1 study)	++00 low[2,3]	Non-significant
Back specific functional status ODI long-term follow-up	The mean pain intensity of the control group was **26.08 points**.	The mean ODI score in the intervention group was **6.38 points lower** (14.98 lower to 2.22 higher).	45 (1 study)	++00 low[1,3]	Non-significant

Table 2.2: Summary of findings of comparison I (perceptual proprioceptive training versus inactive controls or other exercise) *(continued)*

Comparison 1.2	Other exercise	pPrT	N (studies)	GRADE	Comments
Pain intensity various scales short-term follow-up		The mean pain intensity in the intervention group was **1.15 standard deviations lower** (2.93 to 0.63 lower)	80 (2 studies)	000+ very low[2,3,4]	
Pain intensity various scales long-term follow-up	The mean pain intensity of the control group was **4.44 points**.	The mean ODI score in the intervention group was **0.01 points higher** (1.55 lower to 1.57 higher).	45 (1 study)	++00 low[2,3,§]	
Back specific functional status various scales short-term follow-up	The mean ODI score of the control group was **19.04 points**.	The mean ODI score in the intervention group was **0.8 points higher** (5.80 lower to 7.40 higher).	50 (1 study)	++00 low[2,3,§]	
Back specific functional status various scales long-term follow-up	The mean ODI score of the control group was **14.72 points**.	The mean ODI score in the intervention group was **4.98 points higher** (2.68 lower to 12.64 higher).	45 (1 study)	++00 low[2,3,§]	

N = total number of patients; CI = Confidence Interval; [1]Serious limitations in study design (i.e. ¿25% of participants from studies with high risk of bias); [2]Serious imprecision (i.e. total number of participants ¡300 for each outcome or only one study available for comparison); [3]Indirectness of population (e.g. only one study), intervention (applicability) and outcome measures; [4]Serious inconsistency (i.e. significant statistical heterogeneity or opposite direction of effects). [§]Only one study, consistency cannot be evaluated.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

Comparisons II: rPrT versus other exercises or inactivity

Two studies with high risk of bias showed significant group interactions for self-reported pain in favour of the rPrT intervention [57, 71] (Table 2.3). Both compared change of VAS after head-eye coordination exercises with an inactive group of patients with chronic neck pain (MD (95% CI) = -1.6 (-3.6 to 0.3). Co-interventions were not controlled. There is very low evidence (2 RCTs; $N = 103$; limitations in design, imprecision, and inconsistency) that rPrT is more effective in short-term reduction of pain than not intervening at all. One study with low RoB [58] compared a 6-week proprioceptive head-eye coordination program with conventional physiotherapy without PrT elements but found no group differences at 6 weeks follow-up. There is low quality evidence (1 RCT; $N = 58$; limitations in imprecision and indirectness) that there is no difference in short-term effectiveness of rPrT on self-reported pain compared to other exercises. The same RCT [58] compared rPrT to stretching and strengthening exercises and found no group differences on the neck specific functional status using the Neck Disability Index after a 6-week intervention period. There is low evidence (1 RCT, $N = 58$; limitations in imprecision and indirectness) that there is no difference in short-term improvement on functional status between rPrT and other forms of exercise.

Table 2.3: Summary of findings of comparison II (joint repositioning training (rPrT) versus inactive controls or other exercise)

Patient or population: adults with non-specific chronic low-back pain.
Settings: primary and secondary health care centres.

Outcomes	**Illustrative means (95% CI)**		**N (studies)**	**GRADE**	**Comments**
	Control group	**Intervention group**			
Comparison 2.1	**Inactive control**	**rPrT**			
Pain intensity VAS (0 to 10) scales short-term follow-up	The mean pain intensity ranged across control groups from 4.8 to 7.5 points	The mean pain intensity in the intervention groups was **1.6 points lower** (3.6 lower to 0.3 higher)	88 (2 studies)	+000 very low[1,2,4]	
Comparison 2.2	**Other exercise**	**rPrT**	**N (studies)**	**GRADE**	**Comments**
Pain intensity Numeric Pain Rating (0-10) short-term follow-up	The mean pain intensity of the control group was reduced by **2.8 points**.	The mean pain intensity in the intervention group was **0.90 points higher** (0.16 lower to 1.96 higher).	58 (1 study)	++00 low[2,3,§]	
Back specific functional status Neck Disability Index (0-50) short-term follow-up	The mean NDI score of the control group was reduced by **8.4 points**.	The mean NDI score in the intervention group was **1.50 points higher** (2.06 lower to 5.06 higher).	58 (1 study)	++00 low[2,3,§]	

N = total number of patients; CI = Confidence Interval; [1]Serious limitations in study design (i.e. ¿25% of participants from studies with high risk of bias); [2]Serious imprecision (i.e. total number of participants ¡300 for each outcome or only one study available for comparison); [3]Indirectness of population (e.g. only one study), intervention (applicability) and outcome measures; [4]Serious inconsistency (i.e. significant statistical heterogeneity or opposite direction of effects). [§]Only one study, consistency cannot be evaluated.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

Comparisons III: mPrT versus other exercises, inactivity, or behavioural approach

Four studies compared mPrT effects on pain to inactive control groups [59, 74, 62] (Table 2.4). The Taimela study (low RoB) found significant reduction of neck pain [74] immediately after a 12-week multimodal intervention period, but not at the one-year follow-up measurement. However, as this study did not quantify the long-term follow-up of its outcomes on pain and function, it was not included in the synthesis of results. Two other mPrT studies (low RoB) found significant group differences at long-term follow-up after one year [59, 62], but no short-term differences. Only one mPrT study was not biased by co-interventions [60] but had other limitation (sample size and baseline imbalances). Otherwise low in RoB, the study described significant reduction of neck pain after 5 weeks of mPrT whereas pain persisted in the non-exercise control group. There is moderate quality evidence that a multimodal intervention with proprioceptive elements is more effective on pain alleviation at post-treatment than not intervening at all (4 RCTs, $N = 329$; limitations in inconsistency). There is low quality evidence (2 RTCs, $n = 247$; limitations in imprecision and inconsistency) on the effectiveness of mPrT compared to inactive control groups on self-reported pain at long-term follow-up. The Costa study with low RoB showed significant group differences for the RMS functional scale [62] when compared to the placebo control group after the 8-week therapy program. One low RoB study reported no significant group differences for functional status outcomes [59]. The pooled SMD (95% CI) between groups was -1.39 (-2.95 to 0.16). There is low quality evidence (2 RCTs, $N = 246$; limitations in imprecision and inconsistency) that mPrT is more effective compared to inactive or placebo control groups on functional status of LBP patients at short-term assessment. There is moderate quality evidence (2 RCTs, $N = 229$; limitations in imprecision) that mPrT is no more effective compared to inactive controls at long-term follow up. Eight RCTs compared the effects of mPrT with other forms of active treatments and exercises. Significant between group differences in favour of mPrT was found in two high RoB studies immediately after a four-week intervention [73]. Two further studies with high RoB reported significant pain reduction [67, 61] but no more than when the same exercises were performed without additional PrT-elements. The latter findings were confirmed by three low RoB studies where no group differences are reported [65, 64, 74]. One high RoB study [63] reported significant group differences in favour of the control group with no PrT elements. There is low quality evidence (8 RCTs; $N = 465$ and 122 for short- and long-term respectively; limitations in design and inconsistency) that mPrT is more effective than other exercise interventions on reduction of self-reported pain (short or long-term). Comparison of various back specific functional scales showed short-term effects with significant group difference in one study with low RoB [64] and in two further studies with high RoB [73, 61]. There is low quality evidence (8 RCTs; $N = 466$ and 1 RCT with $N = 107$ for short- and long-term respectively; limitations in imprecision and indirectness) on the effectiveness of mPrT on functional restoration. Sorensen et al. [72] tested an educational approach against symptom-based physical training with PrT elements. Similar improvements

were reported after the 8-week intervention period with no long-term improvement in either one of the groups. There is low quality evidence (1 RCT, $N = 185$ and $N = 164$ for short- and long-term respectively; limitations in imprecision and indirectness) that mPrT is no more effective for pain alleviation when compared to an educational method (short or long-term follow-up). Comparison of functional outcomes [72, 74] showed no group differences at short- or long-term assessments. There is low quality evidence (1 RCT, $N = 185$; limitations in imprecision and indirectness) that mPrT is similarly effective as an educational approach to functional restoration of patients with neck or low back pain. There is low quality evidence that (1 RCT; $N = 164$; limitations in imprecision and indirectness) that mPrT is less effective for long-term treatment of CNLBP than the educational approach.

Table 2.4: Summary of findings of comparison III (multimodal proprioceptive Training (mPrT) versus inactive controls, educational approach or other exercise)

Patient or population: adults with non-specific chronic low-back pain.
Settings: primary and secondary health care centres.

Outcomes	**Illustrative means (95% CI)**		**N (studies)**	**GRADE**	**Comments**
	Control group	**Intervention group**			
Comparison 3.1	**Inactive control**	**mPrT**			
Pain intensity various scales short-term follow-up		The mean pain intensity in the intervention group was **0.55 standard deviations lower** (0.98 to 0.13 lower)	329(4 studies)	+++0 moderate[4]	
Pain intensity various scales long-term follow-up		The mean pain intensity in the intervention group was **0.36 standard deviations lower** (0.65 to 0.08 lower)	247 (2 studies)	++00 low[2,4]	+1 study reported no between-group difference (not quantified)
Back specific functional status various scales short-term follow-up		The mean functional status in the intervention group was **1.39 standard deviations lower** (2.95 lower to 0.16 higher).	246 (2 studies)	++00 low[2,4]	+1 study reported no between-group difference (not quantified)
Back specific functional status various scales long-term follow-up		The mean functional status in the intervention group was **0.44 standard deviations lower** (1.80 lower to 0.92 higher).	246 (2 studies)	+++0 moderate[2]	+1 study reported no between-group difference (not quantified)

Table 2.4: Summary of findings of comparison III (multimodal proprioceptive Training (mPrT) versus inactive controls, educational approach or other exercise) *(continued)*

Comparison 3.2	**Other exercise**	**mPrT**	**N (studies)**	**GRADE**	**Comments**
Pain intensity various scales short-term follow-up		The mean pain intensity in the intervention group was **0.40 standard deviations lower** (0.84 lower to 0.05 higher)	465 (8 studies)	++00 low[2,4]	
Pain intensity various scales long-term follow-up	The mean pain intensity of the control group was **35.7 points**.	The mean pain intensity in the intervention group of one study was **13.4 points higher** (5.96 to 20.84 higher).	122 (1 study)	++00 low[2,4]	+1 study reported no between-group difference (not quantified)
Back specific functional status various scales short-term follow-up		The mean pain intensity in the intervention group was **0.45 standard deviations lower** (0.83 to 0.08 lower)	466 (8 studies)	++00 low[2,4]	+1 study reported no between-group difference (not quantified)
Back specific functional status various scales long-term follow-up	The mean pain intensity of the control group was **16.2 points**.	The mean pain intensity in the intervention group of one study was **3.2 points higher** (1.55 lower to 7.95 higher).	107 (1 study)	++00 low[2,3]	+1 study reported no between-group difference (not quantified)
Comparison 3.3	**Educational approach**	**mPrT**	**N (studies)**	**GRADE**	**Comments**
Pain intensity VAS scales (0-10) short-term follow-up	The mean pain intensity of the control group was **4.9 points**.	The mean pain intensity in the intervention group was **0.30 points higher** (0.32 lower to 0.92 higher).	185 (1 study)	++00 low[2,3,§]	
Pain intensity various scales long-term follow-up	The mean pain intensity of the control group was **4.5 points**.	The mean pain intensity in the intervention group was **0.30 points higher** (0.40 lower to 1.00 higher).	164 (1 study)	++00 low[2,3,§]	

Table 2.4: Summary of findings of comparison III (multimodal proprioceptive Training (mPrT) versus inactive controls, educational approach or other exercise) *(continued)*

Back specific functional status LBP rating scale short-term follow-up	The mean score on the LBP rating scale of the control group was **11.6 points**.	The mean pain intensity in the intervention group was **1.40 points higher** (0.33 lower to 3.13 higher).	185 (1 study)	++00 low[2,3,§]
Back specific functional status LBP rating scale long-term follow-up	The mean score on the LBP rating scale of the control group was **11.0 points**.	The mean pain intensity in the intervention group was **2.00 points higher** (0.06 to 3.94 higher).	164 (1 study)	++00 low[2,3,§]

N = total number of patients; CI = Confidence Interval; [1]Serious limitations in study design (i.e. ¿25% of participants from studies with high risk of bias); [2]Serious imprecision (i.e. total number of participants ¡300 for each outcome or only one study available for comparison); [3]Indirectness of population (e.g. only one study), intervention (applicability) and outcome measures; [4]Serious inconsistency (i.e. significant statistical heterogeneity or opposite direction of effects). [§]Only one study, consistency cannot be evaluated.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

Discussion

This SR attempted to provide an overview of current evidence for the use of PrT in rehabilitation of patients with chronic neck- and back pain. Its secondary aim was to identify practical features of PrT strategies that resulted in positive outcomes, i.e. alleviating self-reported pain and improved functional status. The collected data from 18 studies after an extensive search in all relevant databases suggest that no conclusive evidence exists to support the implementation of PrT interventions in back- or neck-pain rehabilitation. On the other hand, most interventions with PrT elements did report some reduction in pain and improvement of functional status, but the methodological approaches do not allow drawing an arrow of causality to either the PrT intervention or defective neuromuscular signalling. With multiple low-quality RCTs reporting conflicting findings on the effectiveness of PrT on pain and functional status, this qualitative analysis cannot provide any conclusive recommendations.

Methodological limitations of included studies

The overall quality of the studies was low and RoB assessment revealed considerate methodological short- comings posing moderate to high risk of bias. Such findings cannot be ignored, particularly in research on subjective outcomes such as pain and functional status [55]. Strong empirical evidence suggests that such violations of fundamental methodological guidelines, e.g. failure to conceal allocation sequence in randomized trials, is associated with overestimation of effects [75]. Solidly performed randomisation allows for the sequence to be unpredictable [76] and if assignments are non-random, deciphering of sequence can occur. Missing outcome data, due to attrition during the study or exclusion from the analysis was apparent in many included reports and may have led to overestimation of effects [76]. A further source of bias often found was baseline imbalance, which might suggest bias in allocation and could cause statistical bias. Thus, differences in outcomes could be due to characteristics of patients rather than treatment [77]. Similarly, it was observed that most studies did not measure proprioceptive outcomes hence diminishing the conclusion to make any connection of the experienced effect on proprioceptive signalling or neuromuscular control [69]. To properly understand the effects of PrT on pain and function, proprioception itself should also be observed, preferably using neurophysiological measurements (e.g. proprioceptive evoked potential [78]). In light of these methodological shortcomings, it is not possible to substantiate or refute the assumption of the superiority of PrT rehabilitation over other approaches.

Recommendations on PrT implementation

Apart from the many definitions of PrT, there are no recommendations or practical cornerstones of an effective PrT. In any exercise, proprioception and other sensory inputs are involved [43, 79]. Moreover, frequency, dosage, and duration are other factors applied in a variable way. Inconsis-

tent use of exercise protocols might lead to potential intervention bias regarding the evidence of optimal training protocols to be used in non-specific musculoskeletal pain [76]. Sample sizes of future trials should be large enough to enable sub group and dose- response analyses. With no standardised procedure of PrT it is impossible to create effective pooling of outcome data. The question on how long PrT would have to be exercised or how often it should be done (e.g. on a daily basis, once every week) and at which intensity cannot be answered in this review.

Limitations

The RoB rating proved to be challenging and relatively high inconsistency between the review authors in one particular item (selective reporting) was apparent. Using standardised scales for rating methodological quality leads to some practical issues. Blinding of therapists and patients is often not possible where the intervention is as obvious as is PrT. The assessment tool by Cochrane addresses this issue in a pragmatic way by allowing reviewers to assess importance of each item and rate level of risk in the context of the field of research. This is at the same time the tool's greatest weakness, as it does not delimit the scale with clear boarders. This may cause incongruences between review authors with different levels of methodological training or content knowledge [55]. Lack of elaborations and clarity in described methods also contributed to the difficulties while rating the quality of the studies. Hence, allocation procedure and sequence generation could not be derived from the provided information in the text. Although several authors were contacted for this reason, the missing information could not be obtained. This lack in reporting quality should be addressed in future studies by explicitly referring to international guidelines, such as the CONSORT statements [75]. Language bias might have led to the exclusion of important findings. One study from Poland and one from Iran (both RCTs) had to be excluded, as no English full texts were available [80, 81]. Meta-analysis could not be conducted on all comparisons and outcome measures due to the methodological and statistical heterogeneity. The attempt to reduce heterogeneity through selected analysis of two further subgroups based on outcomes (e.g. VAS and NRS) and population (neck and back pain) had no effect. Subgroups were clinically still very different from each other, e.g. comparing back pain population receiving perceptive rehabilitation with neck pain population receiving joint repositioning exercise (e.g. [69] vs. [58]). Furthermore, due to the previously mentioned lack of reporting quality, there were insufficient data to report all relevant outcomes required for accurate meta-analyses. A further limitation of the review was delimiting the included interventions. Because of the arbitrary use of expressions (cybernetic exercise, sensorimotor training, etc.), it cannot be guaranteed that all studies addressing PrT were included. There is no consistent term for it. In this sense it may be argued that motor control exercises [62] and perceptive rehabilitation [69] should not have been included in this SR, or, conversely, Saner et al., who assessed movement control exercises in a RCT [82], should have been included. This, however, is one of the reasons it has become so important to conduct a SR on the topic: to collect

the existing information, summarise the evidence, and allow practitioners explain the rational of their interventions. Clearly defining the population and intervention of SR is always difficult in rehabilitation research [52]. The challenge of this particular topic is that it tries to connect two opaque phenomena not fully understood. Sensorimotor changes on spinal and supraspinal level are subject to on-going debates and it is not entirely clear what actually happens on cortical levels when pain becomes chronic [83] and movement behaviour changes [84]. Pain is a complex phenomenon, which, for practical reasons, is often recorded with subjective outcome measures [85] and is not always related to functional impairment. The population included may have a variety of different causes for their pain; hence, function will not necessarily improve when pain does [86]. Verra et al. and Luomajoki et al. have shown how subgroups of fibromyalgia and LBP patients may exist and could respond differently to treatments [87, 88]. Thus, sample sizes of future trials should be large enough to enable subgroups in order to compare CNLBP patients with and without sensorimotor deficiencies. To allow comprehensive and evidence based recommendations for the implementation of sensorimotor exercises (i.e. PrT) there is still need for large scale, high quality RCTs including dose-response analyses based on objective outcome measures of physiological change.

Conclusions

There are not enough interventions conducted in a methodologically solid way to make any conclusive statements on the effects of PrT on pain and function in patients with chronic neck- or LBP. The included studies suggest a tendency towards demonstrable benefits from the PrT intervention, particularly for functional outcomes. Moreover, there is low quality evidence that PrT adds no benefits to conventional therapy. However, findings are inconsistent among different studies. There is low quality evidence that PrT is inferior to educational approaches, which aim at change in behaviour and attitude. Based on the reviewed studies, no recommendations on PrT mode and implementation can be given. Future research on the effect of PrT should try to compare more generalizable samples and clearly define the framework of PrT. Efforts towards a standardised PrT should involve practical experience and incorporate the evidence of basic neurophysiological research. Interventions have to be reported with more care to important details to allow comparison, e.g. group allocation and the definition of proprioception.

Competing interests

The authors declare that they have no competing interests.

Author's contributions

MMC proposed a study protocol, which was elaborated and specified by EdB, BW, and CS. MMC produced an early version of this paper. EdB, BW, and CS substantially revised the paper to bring it to its current form. CS and MMC screened all the references and extracted the data. EdB served as arbitrator in case of discrepancies during extraction. ZS supported the data extraction process. EdB, CS, and MMC interpreted the results. All authors read and approved the final manuscript.

Acknowledgements

We thank Martina Gosteli, University Library Zurich, for her help with formulating and conducting the literature search strategy.

Funding

The authors declare that this research was not subject of any industrial or other type of funding.

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CHAPTER 3

Effects of postural specific sensorimotor training in patients with chronic low back pain: study protocol for a randomised controlled trial

This chapter is based on [1]:

McCaskey, M. A., Schuster-Amft, C., Wirth, B., & de Bruin, E. D. (2015). Effects of postural specific sensorimotor training in patients with chronic low back pain: study protocol for randomised controlled trial. Trials, 16(1), 1-10. http://doi.org/10.1186/s13063-015-1104-4

[1] Figures, tables and language errors in the original publications were corrected for this thesis.

Abstract

Background: Sensorimotor training (SMT) is popularly applied as a preventive or rehabilitative exercise method in various sports and rehabilitation settings. Yet, there is only low-quality evidence on its effect on pain and function. This randomised controlled trial will investigate the effects of a theory-based SMT in rehabilitation of chronic (¿3 months) non-specific low back pain (CNLBP) patients.

Methods: A pilot study with a parallel, single-blinded, randomised controlled design. Twenty adult patients referred to the clinic for CNLBP treatment will be included, randomised, and allocated to one of two groups. Each group will receive 9 x 30 minutes of standard physiotherapy (PT) treatment. The experimental group will receive an added 15 minutes of SMT. For SMT, proprioceptive postural exercises are performed on a labile platform with adjustable oscillation to provoke training effects on different entry levels. The active comparator group will perform 15 minutes of added sub-effective low-intensity endurance training. Outcomes are assessed on 4 time-points by a treatment blinded tester: eligibility assessment at baseline (BL) 2-4 days prior to intervention, pre-intervention assessment (T0), post-intervention assessment (T1), and at 4 weeks follow-up (FU). At BL, an additional healthy control group (n = 20) will be assessed to allow cross-sectional comparison with symptom-free participants. The main outcomes are self-reported pain (Visual Analogue Scale) and functional status (Oswestry Disability Index). For secondary analysis, postural control variables after an externally perturbed stance on a labile platform are analysed using a video-based marker tracking system and a pressure plate (sagittal joint-angle variability and centre of pressure confidence ellipse). Proprioception is measured as relative cervical joint repositioning error during a head-rotation task. Effect sizes and mixed-model MANOVA (2 groups x 4 measurements for 6 dependent variables) will be calculated.

Discussion: This is the first attempt to systematically investigate effects of a theory-based sensorimotor training in patients with CNLBP. It will provide analysis of several postural segments during a dynamic task for quantitative analysis of quality and change of the task performance in relation to changes in pain and functional status.

Trial registration: Trial registry number on cliniclatrials.gov is NCT02304120, first registered on 17 November 2014.

Background

In 2006, the European Cooperation in Science and Technology working group B13 (COST B13) published guidelines for chronic non-specific lumbosacral back pain (CNLBP) treatment reporting a prevalence of CNLBP at 23 % [1]. The State Secretariat for Economic Affairs in Switzerland has released corresponding numbers in the context of preventive measures for occupational settings. According to its author, 18 % of all employees in Switzerland have reported some form of work-related back pain accounting for 26 % of occupational absence with corresponding socio-economic consequences [2]. Although the bulk of the direct costs have been attributed to care by medical physicians and non-physicians, it is the indirect costs through absenteeism and social isolation that cause more than 80 % of health costs [3]. Hence, research promoting return to normal activity and prevention of chronicity of pain remains of great importance.

CNLBP persists for more than 12 weeks and cannot be attributed to a recognisable, known specific pathology (International Classification of Diseases (ICD) 54.5) [1]. Lack of variable sensorimotor input has been described as a contributing factor to the development of CNLBP [4, 5, 6, 7]. In modern society, dynamic movements are becoming ever more neglected and repetitive tasks seem to dominate most of our activities. It has been well-established that occupations requiring prolonged periods of static standing are associated with development of musculoskeletal disorders including CNLBP [7, 8, 9]. Long-term monotonous afferent input is believed to impair the sensorimotor system; circuits regulating the appropriate amount of symmetric muscle force, needed to adapt the correct posture in any given situations, are thought to be disturbed [6, 10, 11]. If not restored, this constant malfunctioning of muscular control and regulation of dynamic movement may lead to inappropriate muscular activity [11, 12] and is thought to contribute to taut muscles, imbalanced muscle activation, poor posture, and ultimately to musculoskeletal pain in lumbar regions [13].

Consequently, neuromuscular rehabilitation techniques addressing sensory deficiencies have emerged in recent years and have received increasing therapeutic attention [6, 14]. These techniques could broadly be summarised as sensorimotor training (SMT) methods aiming at increased proprioceptive input to improve motor response in dynamic environments. This might lead to improved quality of postural control, which in turn may alleviate postural specific musculoskeletal pain [15, 16].

There has been some doubt whether SMT can actually improve proprioceptive acuity in a functional way at all. In a recent review, Ashton-Miller et al. outlined a row of concerns (e.g. lack of neurophysiological evidence) about the validity of current proprioceptive exercises [17]. Although many therapists and clinicians report successful treatment cases, the exact effect and validity of sensorimotor interventions is still discussed controversially [17, 3, 18]. Despite extensive research activity on the topic of CNLBP, which has significantly contributed to the understanding of pain [19], the European guidelines on the management of CNLBP conclude

that the effects of specific exercises, such as SMT, must be further evaluated [1].

The aim of this study is to compare the effects of SMT on pain and functional status with sub-effective low-intensity training (SLIT) in patients with CNLBP: Is a sensorimotor training added to physiotherapy (PT) more effective than physiotherapy with added sub-effective low-intensity training regarding pain and functional status in patients with non-specific low back pain? It is first hypothesised that functional status and self-reported pain will reduce significantly in both groups, but the SMT group will show significantly more improvement when compared to SLIT.

With novel methods available, it has become possible to quantitatively analyse the influence of pain on postural control strategies. Using the uncontrolled manifold approach [20], this study has the secondary aim to describe how much compensatory variability is being applied to maintain the postural control during perturbed stance and whether proprioceptive integration improves with SMT.

Methods/Design

Ethics and reporting

The study protocol follows the Consolidated Standards of Reporting Trials (CONSORT) statement on randomised trials of non-pharmacological treatment [21] and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance for protocol reporting [22]. The procedures have been approved by the local ethics committee (EC North-western Switzerland, EC number: 2014-337) and conform to the guidelines of Good Clinical Practice E6 (R1) and the Declaration of Helsinki. No data was recorded before written informed consent to participate and to publish was given by the participant.

Study design

The SensoriMotor training and Postural control in Pain rehabilitation trial (SeMoPoP) is designed as an assessor-blinded exploratory trial with 2 parallel groups and primary endpoints of pain and functional status before and after the 5-week intervention programme. Additionally, a 4-week follow-up (FU) assessment shall deliver data for intermediate-term effects. Figure 3.1 summarises the study design.

Randomisation, group allocation, and allocation concealment

The randomisation list is stored with the clinic's pharmacy, out of reach and out of sight of the investigator and all treating therapists. The list was computed generated prior to the trial beginning by a third party, who is not involved in patient recruitment, organisation, assessment, or treatment. Mixed randomisation steps were applied using block-wise and simple-randomisation to achieve the unpredictable 1:1 allocation sequence, as has been recommended for smaller group

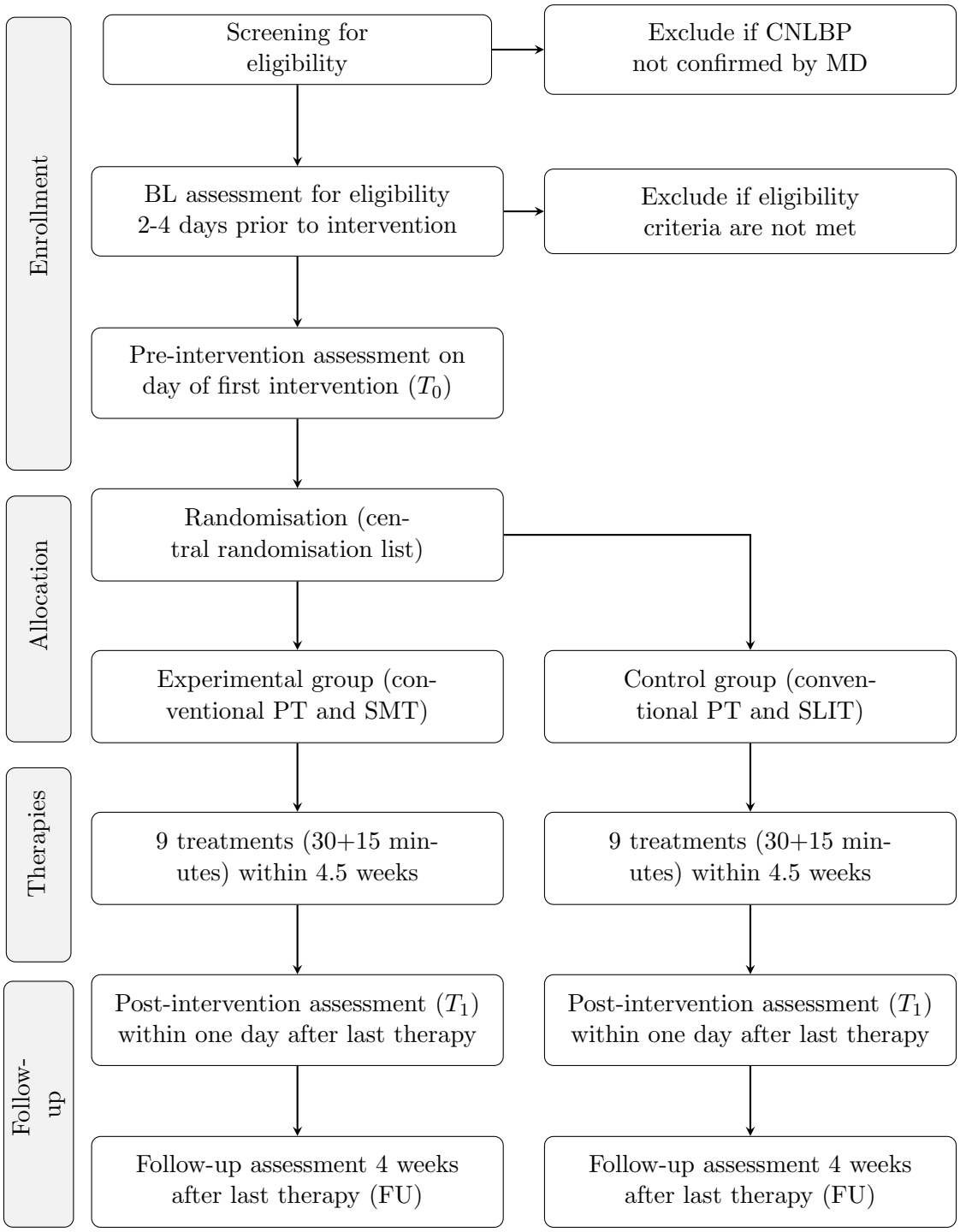

Figure 3.1: Flow chart of study procedures. BL=baseline; PT=physiotherapy; SMT=sensorimotor training; LIT=low-intensity endurance training.

sizes [23]. Prior to the first treatment, the responsible therapist will call the central pharmacy within the clinic to learn the patient's group allocation. Blinding of assessors and data analysts will be maintained until study completion. During statistical analysis, the groups will be referred to without specification of treatment plan (e.g. groups A and B).

Study population

Patients are being recruited from the outpatient department at a neurological and orthopaedic rehabilitation centre in Switzerland. Interventions, assessments and data collection, and data analysis will be conducted at the same study site. Adult patients ($\geq$18 years) referred to the trial clinic for CNLBP treatment by their general practitioner will be invited to participate in the trial. If no medical referral has been given, e.g. as a response to the public invitation in local print media, an independent rheumatologist at the study site will examine the patient for eligibility and to confirm diagnosis (CNLBP). Symptoms included are any chronic (>3 months) pain or discomfort localised below the costal margin and above the inferior gluteal folds, with or without referred leg pain [1]. Written, informed consent must be provided prior to the beginning of any of the study procedures.

Meeting any of the following criteria will lead to exclusion [1, 24]: clinical sign of neurological damage with sensorimotor impairments (i.e. radicular syndrome, paresis or tingling in limbs); suspected or confirmed spinal pathology (e.g. tumour, infection, fracture or inflammatory disease); history of spinal surgery (e.g. decompression or stiffening); whiplash incidence within the last 12 months; cervical pain that reduces active movement to less than 30° rotation to each side; known vestibular pathologies; major surgery scheduled during treatment or FU; physiotherapy with SMT during the last 12 weeks; inability to follow the procedures of the study: e.g. due to language problems, psychological disorders, dementia of the participant; parallel participation in another study; previous enrolment into the current study.

Study intervention

All participating patients will attend 9 sessions of 45 minutes duration consisting of 30 minutes standard physiotherapy according to European guidelines (COST, [1]) with either added experimental (15 minutes SMT) or added control exercise (15 minutes SLIT). Sessions will take place twice a week over a 4.5-week period.

The intensity and duration of SLIT in the control group was deliberately instructed to be lower and shorter than is recommended [25]. This was used as a quasi-sham [26] to control time spent with therapist.

There is a wide variety of ways in which SMT can be performed [14, 15]. For this study, proprioceptive postural training (PPT) will be applied using the neuro-orthopaedic therapy device Posturomed (Haider Bioswing GmbH, Pullenreuth, Germany). The Posturomed consists of a labile platform, with adjustable damped swaying behaviour. Mediolateral and anteropos-

terior sway are increased when the two damping brakes, one at the front and one at the back, are released. This allows three specific configurations with increasing levels of instability. The Posturomed is used for therapy, but has also been used for assessment of postural control [27]. In contrast to most proprioceptive training devices, the exercise plan for PPT is clearly defined, quickly explained to the patient and easily understood [28].

Taking part in the study will not affect the patient's prescribed treatment plan but PPT will not be part of the PT sessions. Other than that, the study protocol does not dictate the PT content or restrict any concomitant care. Detailed documentation of provided treatments will be recorded on therapy documentation sheets. Interventions are described in detail according to the Template for Intervention Description and Replication (TIDieR) guidelines [29], see Table 3.1 on page 62.

Staff eligibility

Only a selected group of therapists at the study site will conduct the intervention. To qualify, therapists must have completed their PT training and show competences in musculoskeletal rehabilitation in patients with low back pain and PPT methods. Competences in these areas will be assumed after completion of internal workshops for the treatment under investigation, led by a certified instructor.

Study outcomes

A treatment-blinded assessor will test patients on four measurement events (ME) (Figure 3.1). The eligibility assessment at baseline (BL) will take place 2-4 days prior to intervention on the patients' first visit to the trial site. Pre- intervention assessment (T0) will be recorded on the day of the first therapy session and post-intervention assessment (T1) within 1 day after the last intervention session at 4.5 weeks. Intermediate-term to long-term effects of the intervention will be assessed at a 4-week FU examination (FU). Apart from primary and secondary outcomes, patient characteristics will be recorded to describe the study sample (age, size, weight, activity level, occupation, other therapies, and medication).

Primary outcomes

With the study's primary aim to determine the effects of SMT on pain and functional status compared to usual treatment of patients with CNLBP, the primary outcomes are intended to record mean change of self-reported pain and related limitations in daily activities from T0 to T1 and T0 to FU. This is in line with recommendations by Deyo et al. for the use of standardised outcomes in clinical research on low back pain [31].

Table 3.1: Description of study interventions based on the TIDieR checklist [29]

Item	Experimental group	Control group
1. Brief name	Sensorimotor training	Sub-effective low-intensity cardiovascular training
2. Why	Sensorimotor control is believed to be impaired in chronic non-specific low back pain. PPT is a well- defined SMT method with standardised applications. PPT is indicated for postural specific back pain, functional instability of weight-bearing joints (e.g. knee or ankle instability), hypermobility, and other postural deficiencies	Physical activity at low intensity is not expected to induce a specific treatment effect to the sensorimotor system [18] but can improve the global perception of well-being and can therefore be recommended as part of CNLBP treatment [30]
3. What materials	PPT uses the Posturomed therapy device [28], which is a labile platform restricted to damped anterior-posterior and mediolateral sway. Patients will receive an exercise diary to record adherence and progress.	Cardio-exercise machines: elliptical cross-trainer, treadmill, stationary bike-ergometer. Patients will receive an exercise diary to record adherence and progress.
4. What procedures	9 therapy sessions each lasting 15 minutes. Therapy instructions advise seven stages of difficulty. On all stages the patient is asked to provoke oscillation by stepping on site. After three steps, the patient must stand still on one leg for 2 seconds before he or she repeats the steps. Difficulty is increased by a) decreasing the damping through release of the breaks and b) through added juggling of a ball during the motor task and trunk rotation (dual-task and divided attention). The next stage is reached once stabilisation in the previous stage is secured. The exercise is repeated for as many times as it can be performed adequately without loosing balance. The moment where sensory depletion is observed by the supervising therapist, the exercise is interrupted. The exercise should be repeated for approximately 15 minutes.	9 therapy sessions each lasting 15 minutes. Choosing either the treadmill, elliptical cross-trainer, or a stationary bike, the patient will be instructed and positioned according to body constitution. Next, patient will be asked to begin the exercise at a comfortable pace where speaking is still possible (Borg scale 6 to 9) and to maintain this intensity for 15 minutes.
5. Who provides	Physiotherapists trained in PPT	Physiotherapists and sport scientists
6. How	Both intervention groups will receive initial instruction by a therapist. The patients will then perform the exercises individually with passive supervision by the therapist (e.g. promoting to next difficulty level).	
7. Where	Both interventions will be performed in the medical training centre for physical exercise within the clinic.	
8.When and how much	During the 4.5-week intervention program, patients will receive 9 sessions of the allocated treatment for 15 minutes each (twice a week). This is added to the 30 minutes of conventional therapy both groups are entitled to according to their physician's referral.	
9. Tailoring	Particularly the conventional therapy will be tailored to the needs and abilities of each individual patient. The therapist may apply any form of active or passive treatment during the first 30 minutes (excluding PPT).	
	Although patients will always start with the easiest level, it is not rigorously prescribed which level they must achieve. Only that they should try to reach sensorimotor depletion as judged by the supervising therapist (i.e. can no longer stabilise all segments at the given level of difficulty).	The low-intensity cardiovascular training is in itself tailored as it requires each patient to train at his or her individual recovery level (Borg 6-9).

CNLBP chronic non-specific low back pain, SMT sensorimotor training, PPT postural proprioceptive training

Functional status

Self-reported impairment in daily activities will be assessed using the German version of the Oswestry Disability Index (ODI-D), which has shown good reliability (r = 0.96) [32] and responsiveness [33]. The ODI consists of ten items related to daily activities (pain, body hygiene, lifting objects, walking, sitting, standing, sleeping, sexual behaviour, social life, and travelling). Each item can be rated from 0 ('no pain during activity or pain getting worse') to 5 ('I cannot do it myself'). The total score is reported in percentage of the total achievable 50 points (from 0 % = minimal impairment to 100 % = bedridden). A change of 8 % is considered as clinically relevant [34].

Pain

Self-reported pain will be assessed using a German version of the Visual Analogue Scale (VAS). The VAS is a 100-mm line with 2 endpoints representing the extreme states 'no pain' and 'pain as bad as it could be'. It has shown to have good re-test reliability (r = 0.94) with a 13-mm difference on the scale to be considered as clinically relevant [34].

Secondary outcomes

The secondary outcomes, joint variation and postural control during perturbed stance on a labile platform, will be measured at each measure event (ME) (BL, T0, T1, and FU) using a combination of several outcome measures described below.

Postural control - centre of pressure

Postural control will be operationalised by measuring the deflection of centre of pressure (CP) recorded during the perturbed stance task. Several CP quantifying parameters have been suggested in the literature [35, 36, 37]. For the purpose of the study, CP 95 % confidence-ellipse area and standard-ellipse area (CEA and SEA) [38] will be analysed to use a measure of magnitude. Approximate entropy will be analysed to quantify the regularity or predictability of the time series, which has been reported to be more sensitive to small changes than magnitude alone [39]. Additionally, the amount of sway roduced during the task, needed to return to a steady state of stationary stance after external perturbation of the base of support, will be reported as area under curve (AUC) of the acceleration of the labile platform.

Postural control - uncontrolled manifold index

To sufficiently describe and rate postural control, a more complex approach will be experimentally applied to this study. The uncontrolled manifold (UCM) analysis is an emerging computational approach to study motor synergies. It is based on the assumption that the central nervous system (CNS) does not control each degree of freedom (DOF) individually but rather

selects a subspace of lower dimensionality (a manifold) that corresponds to a value of a performance variable that needs to be stabilised (i.e. centre of mass, CM). When a task is repeatedly analysed, the variance of the control variables (i.e. joint angles) across the attempts can be partitioned into two components: parallel and orthogonal to the UCM. As shown by Sholz et al. [40], the variance of the performance variable CM orthogonal to the UCM is usually smaller as compared to the variance parallel to it when standing in response to surface perturbation. In other words, the CNS allows relatively high variability of control variables (joint angles) as long as this variability does not cause the CM to move further away from its steady state prior to perturbation. Basically, a UCM spans a subspace consisting of all joint angles that support fast return to stability. Joint angle configurations that lie orthogonal to the UCM lead to a deviation from this stable condition and, therefore, affect the controlled variable. The relation of both subspace values to one another will be reported as the UCM-Index. For detailed description of the application refer to Scholz et al. [20].

Proprioception

To assess conscious proprioceptive acuity, cervical joint repositioning error (C-JRE) will be measured. C-JRE is defined here as the relative error of a blindfolded replication of a verbally instructed head position at 0°, 30°, and 60° in the horizontal plane [41, 42].

Measurement set-up

The experimental set-up consists of a labile platform (Posturomed 202, Haider Bioswing, Pullenreuth, Germany), an attached provocation module with manual 3-cm deflection (Haider Bioswing GmbH, Pullenreuth, Germany), 2 high-speed cameras (Basler acA165-uc, Basler AG, Ahrensburg, Germany), a personal computer with a Windows 8 (Microsoft Inc., Redmond, WA, USA) operating system to which both cameras are attached over a USB3.0 cable, a motion analysis software (Templo v.8.2, Contemplas GmbH, Kempten, Germany), an accelerometer attached to the base plate of the Posturomed, and optical markers to measure segmental joint angle variation and joint motion. For the C-JRE task, a custom 1-size light- weight helmet with an attached laser pointer and retro-reflecting markers was developed. For each head position (60°, 30°, 0°, +30°, +60° rotation) a vertical mark is fixed to a screen facing the subject. Video-based analysis of the joint-angle and marker-position deviation will be conducted. The camera will track the reflecting markers with a spatial resolution of 1024 x 760 pixels and a temporal resolution of 100 frames per second, which has shown to suffice for the purposes of the analyses [43]. The algorithms to track the 15.9-mm reflective markers are included in the motion analysis software. Marker configuration follows the proposed scheme by Scholz et al. [40] with nine sagittal markers (Figure 3.2) and additional two frontal markers to record shoulder girdle and hip girdle lateral flexion and medio- lateral translation: at the corner of the eye, the mastoid process, shoulder (acromion), hip (greater trochanter and anterior superior iliac spine), knee

(lateral femoral condyle), ankle (lateral malleolus), toe, heel and the platform surface. For calibration purposes, fixed geometrical objects with known metrics and fixed angles will be placed onto the labile platform and recorded in the frontal and sagittal plane. Coordinate data of each reflective marker will be filtred at 5 Hz using a bi-directional, second-order, Butterworth digital filter in MatlabTM version R2014b (Mathworks Inc., Natick, MA, USA) [20]. Finally, CP is recorded using the zebris FDM-S pressure plate (60 Hz) (zebris Medical GmbH, Isny im Allg´au, Germany), which is placed on top of the swaying platform. All final analysis algorithms will be implemented and executed in Matlab^{TM} version 2014b for Mac (Mathworks Inc., Natick, MA, USA).

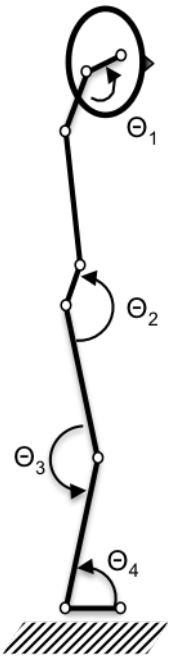

Figure 3.2: Marker configuration. Θ_1 = Cervical angle; Θ_2 = Hip angle; Θ_3 = Knee angle; Θ_4 = Ankle angle; Marker positions (from head to toe): corner of the eye (orbital process of the zygomatic bone), mastoid process of temporal bone, acromion, anterior superior iliac spine, greater trochanter, lateral condyle of femur, lateral malleolus, calcaneal tuberosity, 1st metatarsal bone

Measurement procedures

After interviewing the patient for primary outcomes with the described questionnaires, C-JRE will be tested in a seated position. Wearing a visual deprivation mask and the laser-pointer helmet, the participants will then be verbally instructed to rotate their head slowly. Using the position of the laser on the prepared screen with the marked angles, the assessor guides the participant to reach the target position. This position is held for 15 seconds and subsequently replicated 5 times. Participants are instructed to push a button fixed to the chair when they feel confident to have reached the original position. This will set a marker at the time point

during the recording where the participant felt closest to the initially instructed position and is repeated for every angle. The sequence of angles is randomised prior to the test.

To assess postural control, the patient will first be asked to stand on the platform to familiarise themselves with the surface's behaviour before the platform will be fixed to its deflected position (3 cm posterior). Then the patient will be instructed to adopt an upright posture with arms folded across the chest. On the cue "ready-steady-go", the assessor will release the platform from its deflection. Two familiarisation trials will be performed prior to measurement. The swaying will be recorded in sync with the CP and video for 10 seconds (3 seconds prior to pertubation and 7 seconds after perturbation) and repeated 5 times. All of the device's damping brakes will be released for this test to allow maximal sway and provoke the postural control response. The setup was pilot-tested in order to define optimal settings for the recording (e.g. light, camera distance, marker-repositioning). Each ME will be of approximately 1 hour in duration.

Sample size

Only few studies have investigated the effects of sensorimotor training on pain and functional status. Two of the most recent of these have found significant time and group interactions using the same outcomes. Applying the results of these studies to a sample size calculation with an alpha value of 5 % and the desired power 80 %, it is expected that 10 patients per arm would suffice to reveal group differences and to detect change. Considering these findings and taking into account the explorative approach of this trial, a total number of 40 to 50 participants is planned, including 20 healthy controls for BL-comparison.

Statistical analyses

Baseline comparability of both groups will be inspected for primary and secondary parameters. Mean change and standard deviation of change will be reported as well as mean values of each outcome at every ME. If normally distributed, a mixed (2) Group x (2) ME multivariate analysis of variance (MANOVA) with repeated measures during ME will be conducted for 6 dependent variables (Pain VAS, Functional Status ODI, Postural Control as SEA, AUC, and UCM-Index), and proprioception (C-JRE)). Non-normal distributed data will be analysed with non- parametric methods. Intention-to-treat analyses will be performed. If necessary, an additional per protocol analysis will be carried out. Recorded outcome data of patients who drop out after inclusion will be included in the final analysis (missing data reconstructed based on mean changes and standard deviations of the other participants of the group).

Discussion

The primary aim of this study is to pilot-test a study design and measurement setup to evaluate the efficacy of SMT in the rehabilitation of musculoskeletal pain. As shown in a recent systematic review [14], the justification of SMT in pain rehabilitation is highly questionable from an evidence-based perspective. Moreover, there are no recommendations for dose, frequency or intensity of SMT at which training effects could be expected [14, 25]. With no standardised recommendations regarding its implementation, SMT studies present large practical heterogeneity and can barely be compared systematically. Hence, it remains a vastly under-examined intervention for pain rehabilitation. There is still need for clinical parameters that are sensitive enough to capture small changes in movement behaviour that are expected to improve after or are indicative for SMT. As the aim of chronic pain treatment should be to make the patient feel better and increase quality of life, from a clinical perspective, the most important outcome is the self-reported pain and functional limitations in daily activities. If these outcomes do not improve, the treatment should be adapted to tackle other modalities of pain development. Moreover, pain may change irrespective of the change of the aspect of physical functioning targeted by the intervention (i.e. sensorimotor control) [44]. However, to make a clinically informed decision, it is necessary to know whether symptom development is related to the intervention receiving most attention during the therapy.

One challenge in SMT evaluation lies in the choice of an appropriate parameter to measure change over time or compare different populations. Change could occur at any one level of the complex neural pathway involved in the regulation of peripheral sensory integration. In previous low back pain-related intervention studies, SMT has been assessed using joint repositioning sense [41, 42, 45], CP for postural sway [46, 47] and neurophysiological measures [48]. While JRE only tests one aspect of a single joint involved in the muscle chain of postural control, CP only tests the summation of all joints involved and cannot be dissected to show each segment's contribution [49]. In a reductionist approach, neurophysiological assessments allow investigation of the functions, or dysfunctions, of key elements involved in any given task (e.g. evoked potentials or synaptic activities at neuromuscular junctions and their pathways). Accumulated information of these elements is used to interpret the overlying, more complex system [50]. However, as pointed out by Latash et al., the 'function of a complex system cannot be understood through its structure and the properties of its elements' [50]. Following this notion, one of this study's purposes is not to analyse the effect of chronic pain on individual elements, but rather to examine the dynamic strategies adopted by patients with CNLBP to integrate sensory input when controlling CM under perturbed stance conditions.

The relationship of pain and changes in motor control has been shown in several studies [51, 52, 53, 54, 55] and is seen as a protective reaction of the body to limit provocation of the painful area [56]. The proposed dynamic analysis setup with anticipated perturbation will allow investigation of segmental behaviour at any given moment during stance and allow description of

each segment's contribution to the control of CM when recovering stability. This is an important aspect to not only understand the variability of postural control observed when comparing CNLBP patients with a pain-free population sample, but also to explain within-group variability of CM parameters. Understanding this aspect may help to better target faulty movement strategies and describe its part in underlying mechanisms of pain development.

A challenging limitation of the presented study is going to be the interpretation of the magnitude of variability. Being a relatively young field of research within human kinetics, there are not sufficient findings to describe the optimal amount of variability needed to maintain healthy posture [36, 39, 57]. It is yet to be elicited which degree of variability is necessary to remain adaptive toward external and internal perturbations and at which threshold variability causes deviation from the task's individual goal [39]. Relating joint configurations parallel to the manifold and joint configuration perpetual to the manifold (i.e. UCM- Index) offers a potential evaluation of individual movement quality. As the former causes the CM to return to the point before perturbation while the latter describes the amount of joint configurations causing deflection from initial CM position, a high index would be desirable. Provided the setup proves to be robust enough to record sensitive changes after postural specific SMT and differences across population, a large-scale clinical trial with large sample sizes for both groups could be conducted to identify optimal levels of both components during postural control. This would also allow subgroup-analysis; it is widely accepted that subgroups of patients with CNLBP exist, e.g. with or without movement control impairments [58] or with different risk profiles [59]. The population included may have a variety of different causes for their pain. Hence, function or postural control will not necessarily improve when pain does and vice versa. However, due to its explorative nature, this trial has a limited sample size which would not allow subgrouping [60].

A general limitation to therapeutic trials involving exercise is the limited possibilities to blind the patients from knowing the experimental arm. This is particularly problematic in studies where subjective pain measures are evaluated. To reduce the risk of detection bias, all assessors and data analysts will be blinded to the intervention allocation.

To allow comparability of the conventional PT, a detailed documentation of all exercises and treatment applied during a session will be recorded. However, as the study includes out-patients, it is not controlled regarding what kind of leisurely activities and possible exercises are conducted. In this sense, co-interventions cannot be controlled. If proven feasible and effective, the study will provide an objective, quantifiable and sensitive clinical assessments and a standardised procedure for SMT to implement in a large-scale study.

Competing interests

The authors declare that they have no competing interests.

Author's contributions

MM, EB, BW, and CS developed the research question under MM?s lead. MM developed the study design and measurement setup while EB, BW, and CS acted as methodological councils. MM proposed the study protocol, which was edited and improved by EB, BW, and CS. MM produced an early version of this paper. EB, BW, and CS substantially revised the paper to bring it to its current form. All authors have read and approved the final manuscript.

Acknowledgments

The authors wish to thank Dr Rasev for his valuable time put into an introduction to the pathophysiological model of postural specific low back pain and its related treatment methods using sensorimotor training. The study can only be performed thanks to the diligent and dedicated support of the clinic?s out-patient physiotherapy department: specifically, Sabrina Naegelin, Christian Seibt and Felix Mauch have provided guidance for important clinical aspects to the trial?s intervention. The contributions to improve data acquisition from Dr Rolf van den Langenberg, Michelle Anliker, and Michael Preiswerk significantly increased the reliability of the motion tracking setup and should also be acknowledged. The study is partially funded by a grant from the cantonal department of health and social services of the Canton of Argovia, Switzerland.

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CHAPTER 4

Dynamic multi-segmental postural control in patients with chronic non-specific low back pain: A cross-sectional study

This chapter is based on [1]:

McCaskey, M. A., Schuster-Amft, C., Wirth, B., & de Bruin, E. D. (2016). Dynamic multi-segmental postural control in patients with chronic non-specific low back pain: A cross-sectional study. Submitted to Clinical Biomechanics (October 2016).

[1] Figures, tables and language errors in the original publications were corrected for this thesis.

Abstract

Background: To quantify functional instability in patients with chronic non-specific low back pain (CNLBP), summary scores, e.g. center of pressure (CP), are frequently reported. However, such scores may not reflect the true postural status.

Methods: In this cross-sectional study, summary scores and multi-segmental postural outcomes were compared during a dynamic postural control task in patients with CNLBP (n=24, 24-75 years, 9 females) and symptom-free controls (n=34, 22-67 years, 11 females). Anticipatory postural adjustment was analysed 1 second prior to perturbation. Compensatory postural adjustment was analysed during the first second and from 1 to 3 seconds after perturbation. Postural scores were correlated with health related outcome measures (pain and function). Non-parametric tests for group comparison followed up with P-adjustment for multiple comparisons were conducted. Principal component analysis was applied to reduce dimensionality for kinematic analysis of multiple joints.

Findings: Both groups, on average, performed similarly with respect to the summary outcomes. Comparison of multi-segmental joint kinematics demonstrated significant differences of hip angle excursion (P <0.001) during the response phases, representing medium-sized group effects (r's=0.3-0.4). Significant ($P's$ <0.05), but moderate correlation of CP (r=0.41) and centre of mass trajectory (r=0.42) with the health related outcomes were observed during the anticipatory phase.

Interpretation: These findings lend further support to the notion that summary outcomes do not suffice to describe subtle postural differences in CNLBP patients with low to moderate pain status. During kinematic postural assessments, excessive motion of hip and neck segments should be monitored.

Introduction

Chronic non-specific low back pain (CNLBP) is a highly prevalent (23%) symptom causing troubling socio-economic burdens through direct or indirect costs [1]. Despite recent advances towards understanding the underlying mechanism, CNLBP remains a disabling condition limiting daily activities of affected people [2]. As CNLBP cannot be attributed to a recognizable, specific pathology [1], researchers have tried to identify postural abnormalities in patients with CNLBP as a possible factor in its etiology [3]. Postural control is a particularly common outcome reported in assessments to quantify functional instability associated with pain or prescribe appropriate treatments [4, 3]. However, there have been highly inconsistent findings regarding its validity [4, 3].

Postural control involves complex regulatory feedback systems which rely on continuous and non-corrupted signaling of afferent information [5, 6]. Lack of dynamic and variable sensorimotor input has been described as a possible origin of CNLBP, as it could impair sensorimotor accuracy needed to adapt the correct posture in a variable environment [7, **?**]. From neurophysiological findings it is known that trunk muscle activation patterns change with low back pain (LBP), leading to altered postural responses with potentially pain exasperating consequences [8]. Addressing the issue of causality, a series of studies have shown reduced adaptability of postural control strategies in young LBP patients. In a longitudinal 2-year follow-up study it was found that symptom-free participants with postural strategies similar to LBP patients were at greater risk to develop CNLBP [9]. Recently identified reorganizations of specific sensorimotor areas associated with the performance of a dynamic postural control task [10] lend further support to earlier theories by Janda [7], who claims that people with coordination difficulties are more likely to develop pain.

Postural control is defined as the ability to coordinate all segments of the body to maintain control of the body's center of mass (CM) in relation to the base of support [6]. Whereas an overwhelming majority of findings suggest changes in postural control associated with LBP, it remains disputable whether the use of singular outcomes, such as center of pressure (CP), can capture the complexity of this motor task [3]. Reducing postural reactions to single outcomes, such as CP may not reflect postural strategies, which vary greatly between individuals [11, 12]. This has led to a number of studies investigating multi-joint coordination patterns using kinematic synergies to deal with the redundancy problem and account for its functional advantage, i.e. adaptive flexibility through redundancy [13, 14]. One such method is the uncontrolled manifold analysis (UCM), which allows linking of multi-dimensional elemental variables to a one-dimensional performance variable [13, 15]. UCM is based on the idea that the central nervous system (CNS) does not control the exact movement of every peripheral joint segment. Instead, it merely tries to limit undesirable variation in segmental configuration which would impair the accuracy of the desired goal (nonmotor equivalent). In terms of postural control, the goal would be to maintain the CM within the area of base of support by limitation of all

possible joint configurations deviating from this goal [15, 13]. Providing a manifold of solutions that agree with the endpoint (motor equivalent variability), the UCM approach offers a solution to the problem of inverse kinematics where an under-defined system with more than one solution must be analysed.

It is not until only recently that multi-segmental analysis of postural control with UCM has been applied to pathological conditions [16, 17]. In an analysis of a sit-to-stand task, Tajali et al. found significantly lower motor equivalence in CNLBP [18]. However, it remains unclear how chronic pain may affect strategies underlying the control of the CM while standing upright. The primary goal of the present study was, therefore, to use UCM as an indicator of how the flexibility of a predefined set of sagittal joint-configurations promote the stability of the CM position in an postero-antero swaying task on a labile platform. It was hypothesised that CNLBP patients would have similar CM trajectories as symptom-free controls but proportionally more nonmotor equivalent segmental variability, i.e. a lower relative ratio of variance components (UCM index, UI).

Methods

The procedures of this cross-sectional study have been approved as part of a larger trial by the local ethics committee (EC North-Western Switzerland, EC number: 2014-337). The study conforms to the guidelines of Good Clinical Practice E6 (R1) and the Declaration of Helsinki (2013). No data was recorded before written informed consent was given by the participants. The trial has been registered and its protocol published [19].

Study population

Upon public announcement, adult pain-free controls and patients ($\geq$ 18 years) with confirmed symptoms of CNLBP presented for assessment at the study site, a rehabilitation center in Switzerland. Included patients reported enduring pain symptoms localized primarily below the costal margin and above the inferior gluteal folds for more than 3 months [1]. Patients were excluded if they presented with nerve root pain or specific spinal pathology (e.g. infection, tumor, fracture). Further exclusion criteria were: history of spinal surgery (e.g. decompensation); whiplash incidence within the last 12 months; known vestibular pathologies; inability to follow the procedures of the task. Participants of the control group confirmed to be pain-free with no limitation in all areas of daily activity. Age, weight, and pain levels were recorded for all participants (Table 4.1).

Procedures

Postural control was assessed on a labile platform fixated at 3cm deflection in posterior direction (Posturomed^{TM}, Haider Bioswing GmbH, Pullenreuth, Germany). Upon manual release, the

	Units	Symptom-free group (N=34, 9 female)		CNLBP group (N=24, 11 female)	
Age (range)	years	39.5	(22-67)	53.2	(24-75)
Height (SD)	cm	171.2	(9.2)	171.6	(10.0)
Weight (SD)	kg	68.3	(11.0)	71.4	(11.2)
VAS (SD)	%	0.0	(0)	28.9	(22.2)
ODI (SD)	%	0.0	(0)	20.1	(10.1)

Table 4.1: Mean and range values for characteristics of the study population. CNLBP: Chronic non-specific low back pain; SD: Standard deviation; VAS: Visual Analogue Scale for self-reported pain; ODI: German version of the Oswestry Disability Questionnaire

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platform sways predominately in anteroposterior direction restricted to the horizontal plane. All of the device's damping brakes were released to allow maximal sway and provoke sufficient postural response. Participants were instructed to adopt an upright posture with arms folded across the chest, feet pointed in a natural stance and gaze fixed on a black dot straight ahead. On the cue 'ready-steady-go', the assessor released the platform. Subjects were asked to react naturally to this anticipated perturbation, as they would do when standing in a vehicle coming to a slow stop. Two familiarisation trials were performed prior to the five measurement trials.

Study equipment

Two-dimensional marker trajectories in space were collected at a sampling frequency of 100Hz by two cameras for frontal and sagittal view (1200x720 spatial resolution) [20, 21]. Motion data was recorded with Templo v.8.2 (Contemplas GmbH, Kempten, Germany). Eight sagittal retroreflective markers were applied (Fig. 4.1): mastoid process, acromion, hip (greater trochanter and anterior superior iliac spine), knee, ankle, and toe. Finally, CP was recorded using the Zebris FDM-S pressure plate (sampling frequency 60 Hz, Zebris Medical GmbH, Isny im Allgäu, Germany), which was placed on top of the swaying platform. All final analysis algorithms were implemented and executed in Matlab^{TM} version R2014b (Mathworks Inc., Natick, MA, USA).

Data processing

Video data and CP data were synchronised using timestamps of the recordings captured with a custom written system tracking program on Python (python.org). Data was aligned along the moment of perturbation. Perturbation was identified as first anteroposterior displacement of the reference marker fixed to the platform. The recording of the data startet shortly before the assessor released the platform and stopped automatically after ten seconds. To ensure same length of all recordings between and within subjects, each recording was trimmed to one second pre-perturbation and three seconds post-perturbation. These four seconds were split into three phases: minus one second to perturbation for anticipatory postural adaptation phase

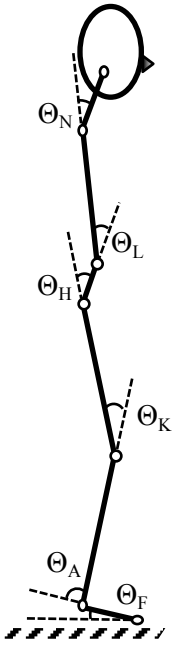

Figure 4.1: Θ_N = Neck angle; Θ_L = Lumbar angle; Θ_H = Hip angle; Θ_K = Knee angle; Θ_A = Ankle angle; Θ_F = Foot angle; Marker positions (from head to toe): corner of the eye (orbital process of the zygomatic bone), acromion, anterior superior iliac spine, greater trochanter, lateral condyle of femur, lateral malleolus, 1st metatarsal bone

(APA) followed by one second of compensatory postural reaction (CPA1) and two seconds of postural re-adaptation (CPA2)[15, 17]. Coordinate data of each reflective marker were filtered at 5 Hz using a bi-directional, second-order, Butterworth digital filter [12]. For calibration purposes, fixed geometrical objects with known metrics and fixed angles were placed onto the labile platform and recorded from both perspectives.

Joint angles and center of mass excursion

As shown in Fig. 4.1, the sagittal marker coordinates were used to calculate the joint angles of the foot (θ_F), ankle (θ_A), knee (θ_K), hip (θ_H), lumbar (θ_L) and neck (θ_N) [6]. Based on estimated segmental CM and mass proportions, weighted sagittal plane CM location was computed for every frame [6]. A geometrical model relating the CM to the joint configuration with origin at the toe was expressed through a trigonometric analysis (equation 4.1):

$$
\begin{aligned}
CM_x(x_{toe}, l_i, \theta_i) = {} & m_1 * (x_{toe} + d_1 * l_1 * cos(\theta_F)) + \\
& m_2 * (x_{toe} + l_1 * cos(\theta_F) + d_2 * l_2 * cos(\theta_F + \theta_A)) + \\
& m_3 * (x_{toe} + l_1 * cos(\theta_F) + l_2 * cos(\theta_F + \theta_A) + \\
& \quad d_3 * l_3 * cos(\theta_F + \theta_A + \theta_K)) + \\
& m_4 * (x_{toe} + l_1 * cos(\theta_F) + l_2 * cos(\theta_F + \theta_A) + \\
& \quad l_3 * cos(\theta_F + \theta_A + \theta_K) + d_4 * l_4 * cos(\theta_F + \theta_A + \theta_K + \theta_H)) + \\
& m_5 * (x_{toe} + l_1 * cos(\theta_F) + l_2 * cos(\theta_F + \theta_A) + \\
& \quad l_3 * cos(\theta_F + \theta_A + \theta_K) + l_4 * cos(\theta_F + \theta_A + \theta_K + \theta_H) + \\
& \quad d_5 * l_5 * cos(\theta_F + \theta_A + \theta_K + \theta_H + \theta_L)) + \\
& m_6 * (x_{toe} + l_1 * cos(\theta_F) + l_2 * cos(\theta_F + \theta_A) + \\
& \quad l_3 * cos(\theta_F + \theta_A + \theta_K) + l_4 * cos(\theta_F + \theta_A + \theta_K + \theta_H) + \\
& \quad l_5 * cos(\theta_F + \theta_A + \theta_K + \theta_H + \theta_L) + \\
& \quad d_6 * l_6 * cos(\theta_F + \theta_A + \theta_K + \theta_H + \theta_L + \theta_N))
\end{aligned}
\tag{4.1}
$$

where m_i is the i^{th} segment proportional mass expressed as percentage of total body mass, l_i is the i^{th} segment's length, d_i is the distal distance from the CM of the i^{th} segment expressed as a percentage of its length, where $i = (1, ..., 6) = (foot, shank, thigh, pelvis, trunk, neck)$. The joint angles were primarily used to examine the relation of the elemental variables θ_i with the performance variable CM_x. Displacement of CM_x and joint angle excursion were calculated as the approximate integral of their trajectories.

Components of joint angle variability

For the present study a variant of the UCM approach, proposed by Scholz et al. [12], was used. Here, the measure of multi-segmental CM control is evaluated at each instant in time to analyze postural responses in different phases during the postural task (4.2). For every recorded frame the variance of the control variables (i.e. joint angles) across the attempts can be partitioned into two components: parallel and orthogonal to the UCM (see below). The variance of the performance variable CM orthogonal to the UCM is usually smaller as compared to the variance parallel to it when standing in response to surface perturbation [12]. Both components of joint angle variability were computed to quantify the amount of variability causing unwanted change (nonmotor equivalent) and the amount of variability returning the CM to its steady-state position (motor equivalent). The relative ratio of both components was reported to allow group-wise comparison. To obtain the variance of both components, the following steps were applied [12]:

1. Create geometric model (Eq. 1).

2. Compute reference joint-configuration based on mean joint configuration during 1 second prior to perturbation.

3. Compute the joint deviation vector (JDV) as the difference between the current joint-configuration and the reference joint-configuration for each segment $\bar{\theta_i}$ at every time-frame of the recording:

$$JDV = \begin{bmatrix} \theta_F - \bar{\theta_F} \\ \theta_A - \bar{\theta_A} \\ \theta_K - \bar{\theta_K} \\ \theta_H - \bar{\theta_H} \\ \theta_L - \bar{\theta_L} \\ \theta_N - \bar{\theta_N} \end{bmatrix} \tag{4.2}$$

4. Linearize the UCM to relate non-commensurate units with different numbers of degrees of freedom through the definition of the Jacobian matrix $J(\theta)$ and the computation of its null space around the reference configuration, $N(J)$.

$$0 = J(\bar{\theta}) * \epsilon_{n-d} = \begin{bmatrix} \frac{\delta CM_x}{\delta \theta_F} & \frac{\delta CM_x}{\delta \theta_A} & \frac{\delta CM_x}{\delta \theta_K} & \frac{\delta CM_x}{\delta \theta_H} & \frac{\delta CM_x}{\delta \theta_L} & \frac{\delta CM_x}{\delta \theta_N} \end{bmatrix} * \epsilon_{n-d} \tag{4.3}$$

$$N = \begin{bmatrix} \epsilon_{1F} & \epsilon_{2F} & \epsilon_{3F} & \epsilon_{4F} & \epsilon_{5F} \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ \epsilon_{1N} & \epsilon_{2N} & \epsilon_{3N} & \epsilon_{4N} & \epsilon_{5N} \end{bmatrix} \tag{4.4}$$

where ϵ_{n-d} are the basis vectors of the null space (n is the number of elemental variables and d is the number of dimensions of the performance variable) representing the linear subspace of all joint-configurations that leave the CM_x position unchanged.

5. Decomposition of the JDV projection into the null-space ($\theta_{||}$ and into its orthogonal space $\theta_{\perp}$:

$$\theta_{||} = \sum_{i=1}^{n-d} \Big(N(J))_i^T \cdot JDV \Big) N(J)_i \tag{4.5}$$

$$\theta_{\perp} = JDV - \theta_{||} \tag{4.6}$$

The computed scalar values represent the length of projection to quantify the consistency of the instantaneous joint configuration with the steady-state configuration.

6. Calculate variance normalised to the number of degrees of freedom $(n-d)$ and trial length (N):

$$\sigma_{||}^2 = \frac{\sum_{i=1}^{N} \theta_{||}^2 N}{(n-d)N} \tag{4.7}$$

$$\sigma_{\perp}^2 = \frac{\sum_{i=1}^{N} \theta_{||}^2 N}{dN} \tag{4.8}$$

7. Calculate relative variance as UCM-index (UI):

$$UI = \left(\frac{2\sigma_{||}^2}{\sigma_{||}^2 + \sigma_{\perp}^2} \right) - 1 \tag{4.9}$$

Center of pressure

Several CP quantifying parameters have been suggested in the literature [3]. For the purpose of this study, CP 95 % confidence-ellipse area (CEA) [22] was analysed as a measure of magnitude. Approximate entropy (ApEn) with dimensionality 2 and a tolerance of 0.2 times the standard deviation was analysed to quantify regularity of the time series, which has been reported to be more sensitive than magnitude alone [23].

Pain and functional status

Self-reported impairment in daily activities was assessed using the German version of the Oswestry Disability Index (ODI-G) [24]. The ODI-G has shown to be a valid and reliable tool to assess functional status in a German-speaking study population [25]. The total score is reported in percentage of the total achievable 50 points (from 0%=minimal impairment to 100%=bedridden). Additionally, self-reported pain was recorded on a 100mm Visual Analogue Scale (VAS) with two endpoints representing the extreme states 'no pain' and 'pain as bad as it could be'.

Statistical analysis

Average values over five trials were used for kinematic and kinetic variables. Multivariate normality and homogeneity of variance was tested and had to be refuted. Hence, non-parametric comparison of two independent groups was computed using the Mann-Whitney-U statistics. Level of significance of primary outcomes was adjusted for multiple comparisons using the Benjamin-Hochberg method [26]. Secondary outcomes (CEA, and ApEn) were analysed in an explorative approach using independent t-tests without adjustment for multiple testing. To analyse the individual joint segments, principal component analysis (PCA) of the mean raw angles was calculated in order to reduce dimensionality. The principal components were computed from three data matrices of 60x6 for each phase (APA, CPA1, CPA2), i.e., 60 participants and 6 angles.

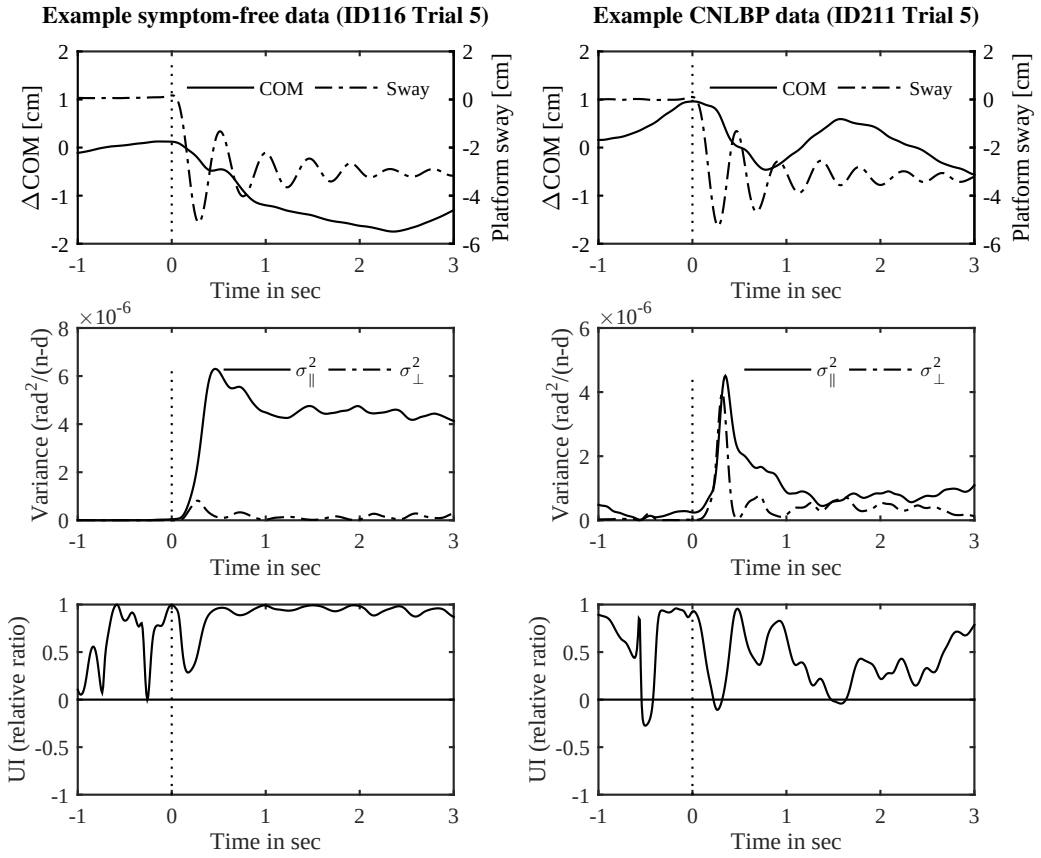

Figure 4.2: Typical data of a high performer (mean $UI_{CPA1} = 0.81$) from the symptom-free control group (left) and low performer (mean $UI_{CPA1} = 0.55$) from the CNLBP group (right). The dotted vertical lines indicate time point of platform release. Top panel shows CM trajectory and actual platform sway trajectory. Middle panel shows normalized variance within and perpendicular to pre-perturbation joint configuration space. Lower panel shows relative ratio of variance.

The percent of cumulated variability explained by each principal component was calculated for each time window. The overall mean PCA values are based on mean absolute PCA values of each participant and presented per group. Correlational effect sizes were calculated for each comparison (r). A one-tailed Pearson correlation was computed to analyse associations of functional outcomes and pain status with dependent variables within the CNLBP group. Averaged values for both groups were statistically analysed in SPSS ($\alpha = 0.05$), release 23.0 (IBM Inc., Chicago, IL, USA).

Results

Primary outcomes: Center of mass and uncontrolled manifold analysis

As had been hypothesised, the kinematic analysis of the CM trajectory showed no significant difference between the groups during any of the analysed phases (Table 4.2). During the initial response phase, the CNLBP group had an average 31.6% higher variance within motor equivalence ($\sigma^2_{||}$), which suggests more joint segment variation while maintaining a stable CM comparable to the control group (U=328,z=-1.263,p=0.21, r=0.2). For both groups, nonmotor equivalence ($\sigma^2_{\perp}$) was significantly smaller than motor equivalence ($\sigma^2_{||}$) indicating the ability to maintain balance throughout the swaying task (Figure 4.3). Accordingly, the relative ratio UI showed no significant difference between the groups for any of the phases.

Secondary outcomes

Primary outcomes: Center of mass and uncontrolled manifold analysis

As had been hypothesised, the kinematic analysis of the CM trajectory showed no significant difference between the groups during any of the analysed phases (Table 4.2). During the initial response phase, the CNLBP group had an average of 31.6% higher variance within motor equivalence ($\sigma^2_{||}$), which suggests more joint segment variation while maintaining a stable CM comparable to the control group ($U = 328$, $z = -1.263$, $P = 0.21$, $r = 0.2$). For both groups, nonmotor equivalence ($\sigma^2_{\perp}$) was significantly smaller than motor equivalence ($\sigma^2_{||}$) indicating the ability to maintain balance throughout the swaying task (Fig. 4.3). Accordingly, the relative ratio UI showed no significant difference between the groups for any of the phases.

Secondary outcomes

Segmental joint angle excursions

Analysis of principal components revealed that the first components, on average, accounted for 92% of the variance in the control group and 95% in the CNLBP group. Table 1 lists the averaged loading of the two principal components and their percentage of variance. The first

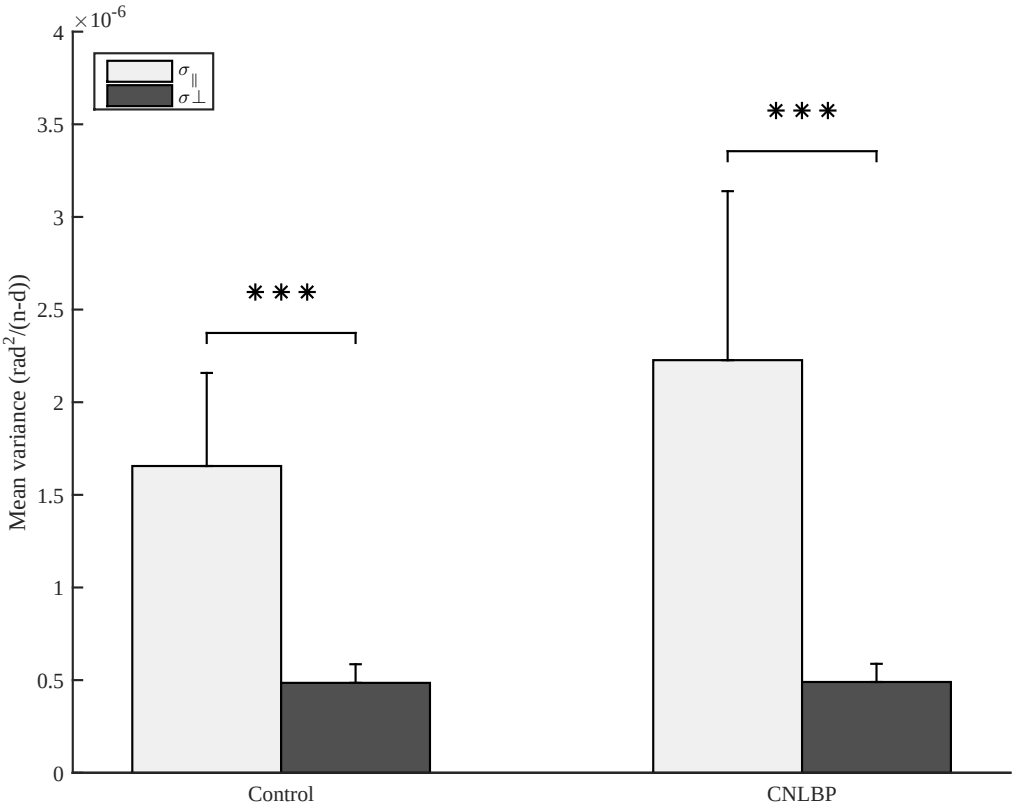

Figure 4.3: Mean variance in the motor equivalent ($\sigma_{||}$) and nonmotor equivalent ($\sigma_{\perp}$) sub-space of the joint deviation after perturbation for both groups. Mean value computed for one second after platform release. Error bars represent 95% confidence interval. $***p < 0.001$

principal component for the CLBP group accounted for 82.4% and 71.2% of the variance for APA and CPA1 phases, respectively. Similarly, the principal component for the control group was responsible for 79.5% and 67.0% of the variance. According to the PCA loadings, the neck and lumbar segments were the principal joints to change the angular position in the APA phase during the response phase, hip segment caused most of the multisegmental movement. This was exploited to reduce dimensionality of the system and allow comparison of just two dependent variables instead of six. The comparison of both groups revealed that mean hip angle excursion of patients with CNLBP (Mdn=0.21 rad) differed significantly from pain free participants (Mdn=0.17 rad, $P = 0.004$) during the initial response phase CPA1, even with the Bonferroni-corrected alpha value of 0.05/6=0.008 (see 4.2). Although a tendency towards more neck angle excursion was observed with a difference of almost 4 degrees during CPA, this effect was not significant ($P = 0.06$).

Center of pressure

The average differences between groups for the linear parameter derived from CP data were negligible and non-significant throughout all phases. However, predictability, i.e. regularity of the signal structure was significantly different after the perturbation. While the ApEn value remained at relatively low level of Mdn=0.35 in the CNLBP group, this value dropped dramatically after perturbation in the control group from Mdn=0.35 at APA to Mdn=0.29 at CPA1 and Mdn=0.27 at CPA2. This represents a significant group difference with $P = 0.03$ (see 4.2).

Functional outcome correlates

The scores of the ODI-D within the CNLBP group were moderately correlated with CM trajectory ($r = 0.42, P < 0.05$) and CEA ($r = 0.41, P < 0.05$) during the APA phase. The VAS score was moderately correlated with the CM trajectory ($r = 0.39, P = 0.03$) during the APA phase. No noteworthy correlations were observed during the response phase. The clinical scores did also not correlate with the primary outcomes UI (max. $r = 0.29$ in CPA2, $P = 0.08$).

Discussion

The presented study shows how differences in postural strategies of a representative sample of CNLBP patients differ on segmental level when compared to symptom-free participants. Both groups are able to maintain a stable CM position after platform release. Joint angles quickly returned to steady-state configuration in both groups, which was reflected by significantly higher variance within the uncontrolled manifold compared to the orthogonal sub-space. This is consistent with previous findings describing control of undesirable deviation of task goals rather than control of each segment to reach that goal [12, 18, 17]. A notably higher degree of motor equivalent variance was observed in the CNLBP group. Although not statistically significant, the

Table 4.2: Main results of primary and secondary outcomes.

	Control Median (Range)	Experimental Median (Range)	U	z	p	r
Primary outcomes						
CM [cm]						
APA	0.28 (0.63)	0.32 (0.47)	358	-0.79	0.43	0.1
CPA1	1.99 (3.46)	2.04 (2.37)	405	-0.05	0.96	0
CPA2	1.97 (3.23)	2.17 (2.27)	288	-1.90	0.06	0.3
UI [ratio]						
APA	0.53 (0.63)	0.51 (0.91)	360	-0.76	0.45	0.1
CPA1	0.40 (0.63)	0.38 (0.49)	382	-0.41	0.68	0.1
CPA2	0.46 (0.86)	0.50 (0.93)	377	-0.49	0.63	0.1
Secondary outcomes						
Hip [rad]						
APA	0.01(0.02)	0.01 (0.01)	379	-0.46	0.65	0.1
CPA1	0.17 (0.26)	0.21 (0.55)	225	-2.89	0.004	$0.4^{\dagger}$
CPA2	0.09 (0.17)	0.03 (0.67)	197	-3.33	< 0.001	$0.4^{\dagger}$
Neck [rad]						
APA	0.01 (0.03)	0.01 (0.12)	293	-1.82	0.07	0.2
CPA1	0.18 (0.35)	0.23 (0.52)	289	-1.88	0.06	0.2
CPA2	0.16 (0.19)	0.17 (0.55)	321	-1.37	0.17	0.2
CEA [cm]						
APA	0.43 (1.44)	0.42 (1.44)	313	-.150	0.13	0.2
CPA1	15.41 (34.54)	16.13 (25.22)	398	-0.16	0.88	0
CPA2	13.49 (24.5)	14.84 (19.66)	337	-1.12	0.26	0.1
ApEn [ratio]						
APA	0.35 (0.36)	0.35 (0.28)	351	-0.90	0.37	0.1
CPA1	0.29 (0.21)	0.35 (0.21)	273	-2.13	0.03	$0.3^{\dagger}$
CPA2	0.27 (0.31)	0.31 (0.38)	269	-2.19	0.03	$0.3^{\dagger}$

Median values of primary and secondary outcomes. U=Mann-Whitney U statistics, z=z-value, p = p-value of between-group difference, r=effect size. † = unadjusted significance for between difference.

medium sized effect underlines the additional effort observed in the CNLBP group to maintain a desirable CM position. Significantly more hip- and notably more head-segment movement was observed in the CNLBP group which was had not been detected by linear CP measures of magnitude (CEA). This is in line with the most recent meta-analysis on CP in CNLBP [3]: unless sensory provocation is applied, e.g. through proprioceptive spindle vibration, CNLBP patients do not present with significantly greater CP trajectories, whether in magnitude nor in structure of the signal.

The observed higher average variance within motor equivalence in the CNLBP group contrasts the findings of Tajali et al. [18], who found significantly lower values in a LBP group during a sit-to-stand task. The group concluded that LBP patients adopted a more rigid strategy during the dynamic phase of the task. The discrepancies may be explained by changes in movement patterns when pain persists for years, as the study population of the presented study were older than in Tajali et al. [18] and, on average, had been suffering from pain for decades. Lower motor equivalent variance in young patients with low levels of CNLBP, observed in Tajali et al. [18], can be explained with well described protective compensation methods in early stages of pain occurrence (e.g. rigid muscle activity with low flexibility) [8, 27]. On the other hand, long-term moderate pain may lead to increased variance, indicative of new postural control strategies adopted to cope with dynamic environments. Too much uncontrolled variance may lead to excessive motion outside the physiological limits of passive structures which stabilise the spine [5], thereby contributing to pain sustenance. This would coincide with the observed increase in total angle excursion with higher pain states presented in this article. The significantly lower ApEn values during the initial response and recovery phases (CPA1 and CPA2) would further substantiate this assumption. As Cavanaugh et al. argue, higher values of ApEn usually represent more complexity and higher variability, which is supposed to be desirable in dynamic environments [28]. It has been shown that within 48 hours after injury, the ApEn value decreases for simple postural tasks. However, upon sudden perturbation of the support surface, certain constraints to susceptible areas may be advantageous. Obviously this would have to be followed up in further studies to be confirmed and to understand the underlying neurophysiological mechanism.

Limitations

Postural control should only be analysed under perturbed, dynamic circumstances [27]. In this sense, it might be argued that for the present study, the perturbation caused by the swaying platform while standing on both legs was insufficient to provoke abnormal responses. But any increase in sway or change to one-leg stand would have failed to represent a functional component of daily activity and impaired standardisation.

Although there was a significant age difference in the observed groups, only a relatively small effect of age on these postural parameters has been described elsewhere [29]. The analysis was

repeated without age-specific outliers and no difference in the results was found. Further caution is advised when comparing the presented findings with similar perturbation studies. In the sit-to-stand task and for the perturbation tasks, the beginning and end of the dynamic phases are clearly defined. In the postural sway task, the participants remain on a labile platform throughout the measurement which means the instability is given throughout the task and only rarely would the exact pre-perturbation configuration be regained. It is therefore difficult to isolate the intrinsic variability from the mechanical effects caused by the swaying platform. It has been shown repeatedly, however, that coordination of joint angles primarily originates from active coordination among the elemental variables [30, 31].

A limitation in marker tracking is the inherent discrepancy from actual joint angles and anatomical reference positions caused by soft tissue deformability and marker positioning accuracy [20, 21]. Using only 2D analysis in the sagittal plane has also been reported to increase the possibilities of errors [21]. However, in cases of movement limited predominantly to one plane results are comparable to 3D analysis [21].

This study presents analysis of the described parameters measured at one point in time. No causal claims are made with regard to the results. Long-term longitudinal studies would allow implications on how motor equivalence and individual joint contribution may change over time and with pain development. The effect of a postural specific intervention on both UCM variance and joint angle excursion would allow description of the direct link between pain, the applied intervention and postural control. Other factors should also be considered, such as fear of falling, exact activity levels, or segmental proprioception.

Conclusion

In conclusion, this study supports the notion that summary outcomes do not suffice to identify postural deficiencies in CNLBP patients and should be applied in combination with multi-segmental analysis. Sustained high signal complexity (ApEn) after perturbation in the CNLBP group suggests an inability to stabilise the susceptible hip region. Significant higher angle variations of the hip segment was needed by patients with CNLBP to maintain similar stability as the symptom-free control group. Yet, CP outcomes and the proposed UI model were not able to identify this difference, suggesting limited clinical use of the measure in patients with CNLBP. When assessing postural control on labile platforms in patients with moderate CNLBP, clinicians using kinematic assessments should observe individual segments with particular attention on excessive hip and neck motion.

Competing interests

The authors declare that they have no competing interests.

Author's contributions

MM, EB, BW, and CS developed the research question under MM's lead. MM developed the study design and measurement setup while EB, BW, and CS acted as methodological councils. MM conducted the analyses and assessments, which were discussed with EB, BW, and CS. MM produced an early version of this paper. EB, BW, and CS substantially revised the paper to bring it to its current form.

Acknowledgements

The authors wish to thank Vivien Gnehm and Maria Emmert, who supported the assessments during their student projects. The contributions to improved data acquisition from Dr Rolf van den Langenberg, Michelle Anliker, and Michael Preiswerk should also be acknowledged. Finally, the critical remarks of Prof. N. Wenderoth have helped to interpret our findings. ProPhysics AG generously provided measurement equipment and counselling for the setup, for which the authors would like to thank Yve Hess and Erwin Schweizer. The study is partially funded by a grant from the cantonal department of health and social services of the Canton of Argovia.

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CHAPTER 5

Postural sensorimotor training versus sham exercise in physiotherapy of patients with chronic non-specific low back pain: A randomised controlled pilot trial

This chapter is based on [1]:

McCaskey, M. A., Schuster-Amft, C., Wirth, B., & de Bruin, E. D. (2016). Added postural sensorimotor training versus added sham exercise in physiotherapy of patients with chronic non-specific low back pain: A randomised controlled trial. Submitted to BMC Medicine (May 2016).

[1] Figures, tables and language errors in the original publications were corrected for this thesis.

Abstract

Background Sensorimotor training (SMT) is popularly applied as exercise in rehabilitation settings. There is only low quality evidence on its effect on pain and function. This study investigated the effects of SMT in rehabilitation of patients with chronic non-specific low back pain (CNLBP).

Methods In this parallel, single-blinded, randomised controlled trial, two arms received 9x30 minutes physiotherapy (PT). The experimental arm received added 15 minutes of postural SMT on a labile platform. The comparator arm performed 15 minutes of added sub-effective low-intensity training (SLIT). A treatment blinded tester assessed outcomes at baseline (BL) 2-4 days prior to intervention, pre- and post-intervention (T0, T1), and at four-week follow-up (FU). Main outcomes were pain (VAS) and functional status (Oswestry Disability Index, ODI). Postural control variables were analysed using a video-based tracking system and a pressure plate during perturbed stance on a labile platform (sagittal joint-angle variability and centre of pressure derived data). Robust, nonparametric multivariate hypothesis testing was performed.

Results 22 patients (11 females, mean age=55 years (32-75), mean (95%CI) pain at BL=22.5% (17.4-27.6%), ODI at BL=18.1% (13.8-22.5%)) were included for analysis (11 per arm). Mean (95%CI) VAS decreased from 24.8% (17.2-32.3%) at BL to 15.6% (3.3-27.9%) at FU in the SMT group, and from 19.9% (12.1-27.7%) to 15.5% (8.8-22.2%) in the control group (p=0.94). Mean (95%CI) ODI decreased from 19.7% (14.4-25.0%) at BL to 8.2% (2.3-14.2%) at FU in the SMT group ($p < 0.01$), and from 16.0% (4.8-27.2%) to 12.3% (7.1-17.5%) in the control group ($p_{within} = 0.39$, $p_{between} < 0.001$). However, group-by-time interaction effects were non-significant (Q=3.3, p=0.07). Secondary kinematic outcomes did not change over time in either of the groups.

Conclusions Despite significant improvement of ODI after SMT, overall findings of this pilot study suggest that, in patients with moderate CNLBP, 9x15 minutes of added SMT as part of prescribed physiotherapy provides no added benefit for pain reduction or functional improvement. Higher doses may be more effective and results may not apply to patients with higher pain levels. Trial registration: ClinicalTrials.gov: NCT02304120. Please see related study protocol, DOI: 10.1186/1471-2474-15-382

Background

Chronic non-specific low back pain (CNLBP) refers to symptoms associated with pain in the lower region of the back that have not subsided spontaneously within 12 weeks and cannot be attributed to any specific physiological cause [1]. Up to 85% of individuals presenting for primary care with low back pain (LBP) are said to be non-specific [2]. A cohort study from 2009 found that 42% of all participants presenting with acute LBP go on to develop CNLBP, in 11-12% to a limiting degree in terms of daily activities [3, 1]. The high prevalence of CNLBP in developed countries (approximately 23 %) has led to innovative treatment methods and exercise programs [1]. Despite these efforts, CNLBP continues to be the leading cause of years lived with disability, substantially weighing down on health care delivery systems and society [4]. Considering the high socio-economic burden caused by the condition, it remains important to monitor the efficacy of interventions [5, 6].

Despite strong evidence for psychological predominance in CNLBP, the importance of mechanical stress possibly aggravating pain cannot be ignored [6]. Taking a non-pathological perspective on the development of CNLBP, Rolli-Salathé et al. [7] list a row of physical resources that appear to be relevant to pain-resilient and pain-free individuals, including more accurate sensorimotor control of the spine and posture. Sustained aberrant posture could likely remain a pocketed origin for pain initiation or persistence caused by connective tissue remodelling, increased local tissue stiffness and central nervous system (CNS) changes [8]. Addressing the issue of causality, a longitudinal 2-year follow-up study has shown that symptom-free participants with reduced postural adaptability were at greater risk to develop CNLBP [9]. Poor motor control in general, and posture in particular, have been clinically and experimentally linked to CNLBP in other studies too, unanimously attesting that poor posture is rather a problem of central coordination than weakness of muscular structures [10, 11, 12, 13]. Hence, the theory of impaired sensory inputs as a key player in the development and preservation of CNLBP has received considerate attention in recent years [14]. Although it comes intuitively that dysfunctional regulating systems (CNS) or executive structures (i.e. muscular system) are reflected in altered motor performance, the existence of actual proprioceptive deficits in patients with CNLBP has not been confirmed [15]. Only recently, however, Pijnenburg et al. found reorganisations of specific sensorimotor areas associated with the performance of dynamic postural control tasks using resting-state functional imaging methods in patients with CNLBP [16].

According to Maki et al. [17], postural control can be defined as the 'process by which the CNS generates the pattern of muscle activity required to regulate the relationship between the centre of mass (CM) and the base of support'. The basic principle of sensorimotor training (SMT) is to emphasise postural control and progressively challenge the sensorimotor system to restore normal control of individual segments during dynamic tasks. The practical application in patients with CNLBP involves simple rehabilitation tools like balance boards or elastic bands to elicit neuromuscular provocation and enhance its adaptation [18, 19, 20]. Within this article,

SMT will henceforth be understood as a postural training on labile platforms aiming at the integration and provocation of afferent signalling during standardised training programs and does not include endurance or hypertrophy training [21]. Although the importance of movement variability and synergies in human motor control is supported by numerous experiments in healthy adults [22, 23, 24, 25], the effectiveness of the many variations of SMT applications and their respective doses, in younger and middle-aged adults, with or without musculoskeletal pain, have yet to be investigated [26, 27]. Such information would allow standardised recommendations for clinical implementation, as has been done for cognitive-behavioural approaches and other exercises [1].

The aim of this pilot study was to compare the effects of SMT on pain and functional status with sub-effective low-intensity training (SLIT) in patients with CNLBP: Is a sensorimotor training added to physiotherapy (PT) more effective than physiotherapy with added sub-effective low-intensity training regarding pain and functional status in patients with non-specific low back pain? It was first hypothesised that functional status and self-reported pain will change significantly in both groups, but the SMT group will show significantly more improvement when compared to SLIT.

Using the uncontrolled manifold (UCM) approach [28], this study had the secondary aim to describe how much compensatory variability is being applied to maintain the postural control during perturbed stance and whether sensorimotor integration improves with SMT. Does the control of the CM in relation to multi-joint coordination improve after SMT in patients with CNLBP? The second hypothesis was that the relative ratio of task-specific to non-specific variability would increase only in the SMT group.

Methods

Ethics and Reporting

The procedures of this randomised controlled study have been approved by the local ethics committee (EC North-Western Switzerland, EC number: 2014-337). The trial has been registered and its protocol published [29]. This report follows the Consolidated Standards of Reporting Trials (CONSORT) statement on randomised trials of non-pharmacological treatment [30]. The study conforms to the guidelines of Good Clinical Practice E6 (R1) and the Declaration of Helsinki (2013). No data was recorded before written informed consent was given by the participants.

Study design

The 'Sensorimotor training and postural control in pain rehabilitation' trial (SeMoPoP) is designed as an assessor-blinded exploratory trial with two parallel groups and primary endpoints of pain and functional status; twice before and once after the five-week intervention

programme (BL, T0, and T1). Additionally, a four-week follow-up assessment provided data for intermediate-term effects (FU) and to reduce the impact of a potential order effect through learning. Figure 5.1 summarises the study design.

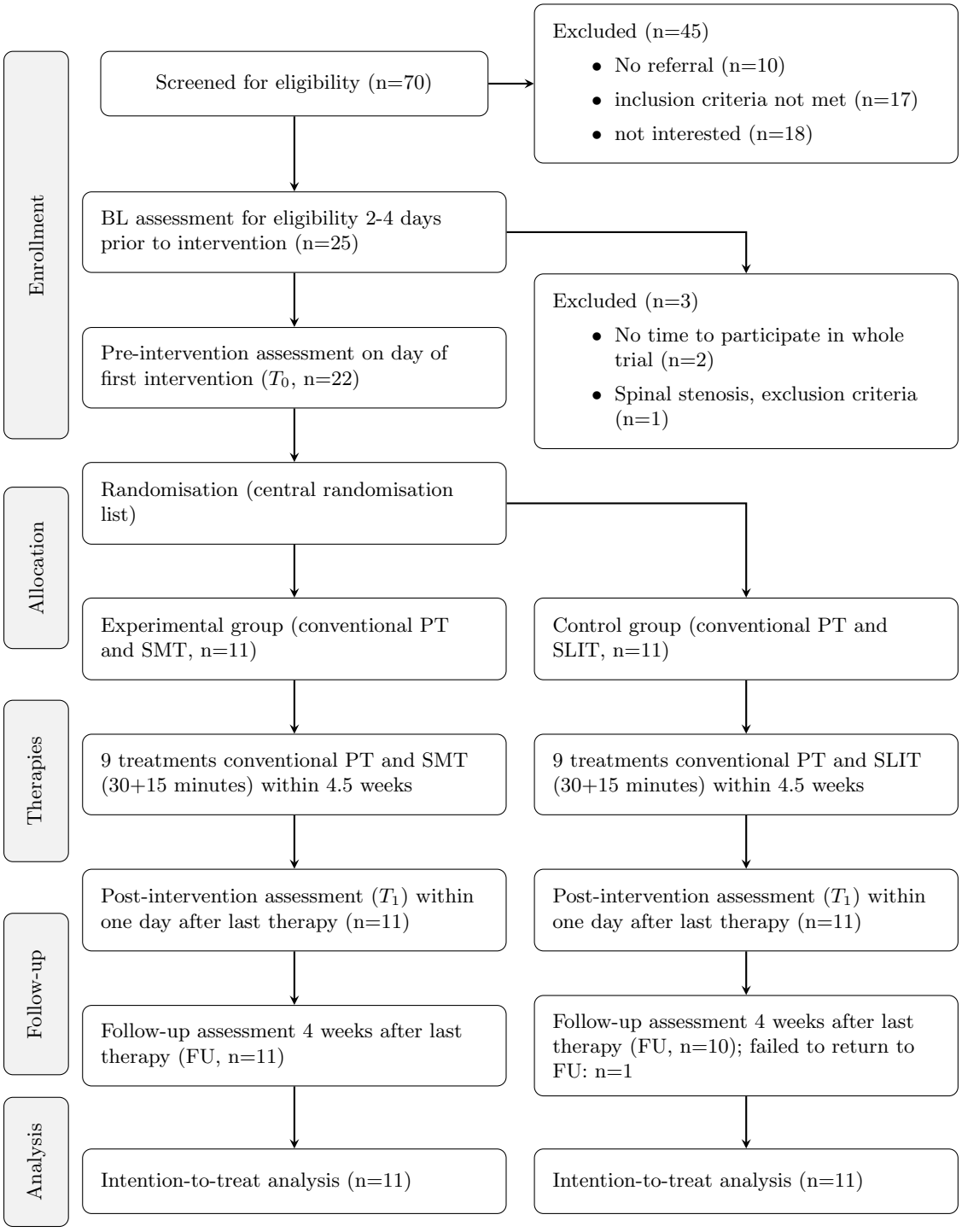

Figure 5.1: Study flow chart: BL=baseline assessment; T0=pre-test, T1=post-test, FU= 4-week follow-up. SMT=sensorimotor training group; SLIT=sub-effective low intensity endurance training group; PT=standard physiotherapy

Table 5.1: Mean, standard deviation and range values for characteristics of the study population.

	Units	Experimental group (N=11)	Control group (N=11)	P value
Gender	f/m	6/5	5/6	0.67[a]
Age (range)	years	55 (32-75)	54 (33-67)	0.99
Height (SD)	cm	172.4 (11.1)	172.8 (7.9)	0.92
Weight (SD)	kg	71.8 (10.5)	72.2 (12.7)	0.94
Activity level	1/2/3*	4/4/3	3/6/2	0.69[a]
VAS at BL (SD)	%	23.9 (7.1)	25.9 (22.8)	0.79
ODI at BL (SD)	%	19.8 (5.3)	17.6 (10.5)	0.55

*PAPRICA defined activity levels (1=inactive, 2=moderately active, 3=trained), a: χ^2 statistics based on cross-tabs

Randomisation, group allocation, and allocation concealment

Randomisation was performed with mixed randomisation steps using block-wise randomisation and simple-randomisation to achieve the unpredictable 1:1 allocation sequence, as has been recommended for smaller group sizes [31]. Prior to the first treatment, therapists contacted the clinic's own pharmacy to learn the patient's group allocation. Blinding of assessors and data analysts was maintained until after study completion. During statistical analysis, the groups were referred to without specification of treatment plan (i.e. group A and B) and only revealed after final analysis was completed.

Study population

Patients were recruited at a rehabilitation centre in Switzerland. Upon public announcement, adult patients (≥ 18) with confirmed symptoms of CNLBP (i.e. with medical referral) presented for baseline (BL) assessment [1]. Included patients reported enduring pain symptoms localised primarily below the costal margin and above the inferior gluteal folds for more than 3 months [2]. Patients were excluded if they presented with nerve root pain or specific spinal pathology (e.g. infection, tumour, fracture). Further exclusion criteria were: history of spinal surgery (e.g. decompression); whiplash incidence within the last 12 months; known vestibular pathologies; inability to follow the procedures of the task or showed unwillingness to continue the trial after BL. To control for any wash-out effects of previous therapies, patients were only invited when they had not been treated for CNLBP for at least 12 weeks. Age, weight, and pain levels as well as activity levels were recorded for all participants (table 5.1). Activity levels were categorised as inactive (=1), moderately active (=2) or trained (=3) according minutes spent active per week and based on recommendations of physical activity promotion in primary care [32].

Study intervention

All participating patients were invited to attend 9 sessions of 45 minutes duration consisting of 30 minutes standard physiotherapy according to European guidelines (COST, [1]) with either added experimental (15 minutes SMT) or added control exercise (15 minutes SLIT). Sessions were scheduled twice a week over a 4.5-week period at the outpatient department of the trial centre. Five trained PT's with advanced SMT knowledge (visited at least one certified SMT course) and at least 2 years of clinical experience conducted the treatments. The intensity and duration of SLIT in the control group was deliberately instructed to be lower and shorter than is recommended [27]. This was used as a quasi-sham to control non-specific effects of time spent with therapists. Taking part in the study did not affect the patient's prescribed treatment plan but SMT was not a part of the PT sessions. Other than that, the study protocol did not dictate the PT content or restrict any concomitant care. Details of provided treatments were recorded on therapy documentation sheets and patient diaries. Interventions are described in detail according to the Template for Intervention Description and Replication (TIDieR) guidelines [33] in the published study protocol [29].

Experimental SMT group: As mentioned above, there are various methods to apply SMT [26, 14]. For this study, proprioceptive postural training (PPT) with the neuro-orthopaedic therapy device Posturomed^{TM} (Haider Bioswing GmbH, Pullenreuth, Germany) was used. The Posturomed consists of a labile platform, with adjustable damped swaying behaviour. Medio-lateral and anteroposterior sway are increased when the two damping brakes, one at the front and one at the back, are released. This allows three specific configurations with increasing levels of instability. The Posturomed is used for therapy, but has also been used for assessment of postural control [34]. In contrast to most proprioceptive training devices, the exercise plan for PPT is clearly defined, quickly explained to the patient and easily understood [35]. Progression of difficulty level and compliance was recorded on a personal exercise diary by the patients and controlled by an exercise therapist at the trial centre.

Control SLIT group: Patients of the control group received additional sub-effective low-intensity cardiovascular training. Physical activity at low intensity for only 15 minutes is not expected to induce a specific treatment effect to the sensorimotor system [36]. Patients were allowed to choose either the treadmill, elliptical cross-trainer, or a stationary bike and were instructed and positioned according to body constitution by an exercise therapist (otherwise not involved in the study). Patients were instructed to exercise at a comfortable pace where speaking is still possible (Borg scale 6 to 9) and to maintain this intensity for 15 minutes. Adherence and settings were recorded in their exercise diary after every visit.

Study outcomes

Pain and functional status

Self-reported impairment in daily activities was assessed using the German version of the Oswestry Disability Index (ODI-G) [37]. The ODI-G has shown to be a valid and reliable tool to assess functional status in a German-speaking study population [38]. The total score is reported in percentage of the total achievable 50 points (from 0% = minimal impairment to 100% = bedridden). A change of $\geq$ 8% is interpreted as clinically relevant [39]. Additionally, self-reported pain was recorded on a 100mm Visual Analogue Scale (VAS) with two endpoints representing the extreme states 'no pain' and 'pain as bad as it could be'. The VAS will also be reported in percentage of line length with a change of 13% interpreted as clinically relevant [39].

Postural control

Many studies have highlighted the importance of all major body segments to stabilise the CM [40, 41, 28]. Applying the UCM analysis, multiple findings of recent studies on human posture have shown that the CM seems to be a task-relevant variable during sit-to-stand tests and quiet stance as it seems to be more controlled than the joint configuration itself [41, 28]. UCM analysis is gradually finding its application in rehabilitation [22, 42, 43]. It is attractive for this purpose because it exploits the redundant properties of the human movement system [42]. Taking into account the number of independent elements of the body (several degrees of freedom) used to achieve a specific result (one degree of freedom), the UCM analysis allows quantification of observations of human movement variability by separating the observed variability into either motor equivalent (does not cause deviation from targeted movement goal) or non-motor equivalent (variability causes deviation from targeted goal). Motor equivalent variability, to a certain extent, is desirable and natural, as it allows compensation of unexpected errors within the movement system [25, 24]. This has been observed to be achieved by synergistic muscle activation and joints acting cooperatively due to intrinsic and developed actions (i.e. natural tendency of inter-limb coordination patterns and experience) [44].

Postural task: The postural control task was conducted on a modified Posturomed with a centrally mounted provocation module that allowed fixation at 3cm deflection in posterior direction (Figure 5.2). Upon manual release, the platform swayed predominately in anteroposterior direction. Participants were instructed to adopt an upright posture with arms folded across the chest, feet pointed in a natural stance and gaze fixed on a black dot straight ahead. On the cue 'ready-steady-go', the assessor released the platform. Subjects were asked to react naturally to this perturbation, as they would do when standing in a vehicle coming to a slow stop. Two familiarisation trials were performed prior to the measurement. A beep signalled the end of the 10 second measurement. This was repeated five times for every participant. All of the device's

damping brakes were released to allow maximal sway and provoke sufficient postural response. To capture the immediate response to the anticipated perturbation, the analysis of the kinematic outcomes was limited to the initial response phase one second immediately after platform release (Figure 5.3).

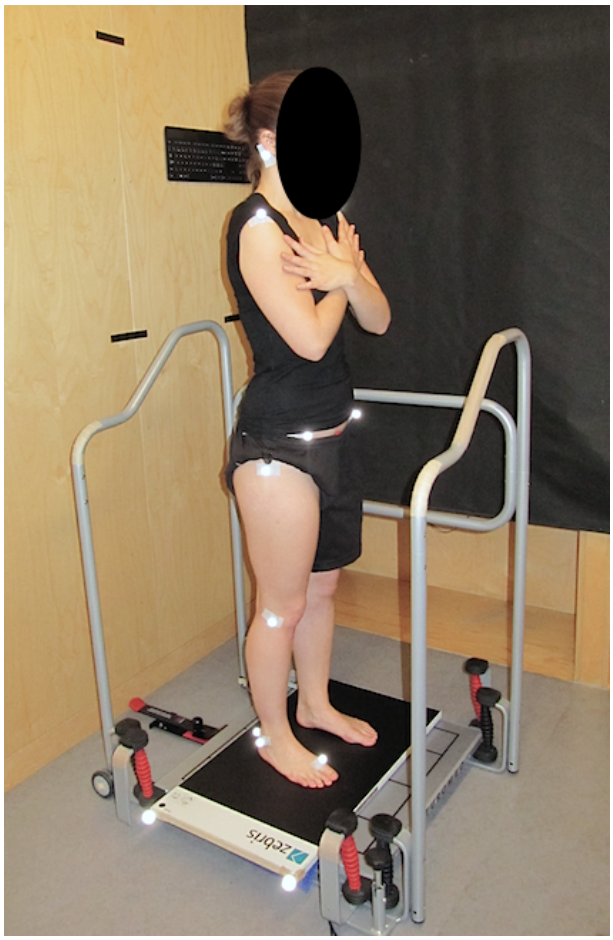

Figure 5.2: Experimental setup: Swaying platform with provocation module and remote triggering from keyboard on wall.

Measurement equipment: Two-dimensional marker trajectories in space were collected at a sampling frequency of 100Hz by two cameras for frontal and sagittal view (1200x720 spatial resolution) [45, 46]. Motion data was recorded with Templo v.8.2 (Contemplas GmbH, Kempten, Germany). Eight sagittal retroreflective markers were configured as depicted in Figure 5.4: the mastoid process, shoulder, hip (greater trochanter and anterior superior iliac spine), knee, ankle, and toe. Coordinate data of each reflective marker were filtered at 5 Hz using a bi-directional, second-order, Butterworth digital filter in Matlab^{TM} version R2014b (Mathworks Inc., Natick, MA, USA) [28]. For calibration purposes, fixed geometrical objects with known metrics and fixed angles were placed onto the labile platform and recorded from both perspectives. To control

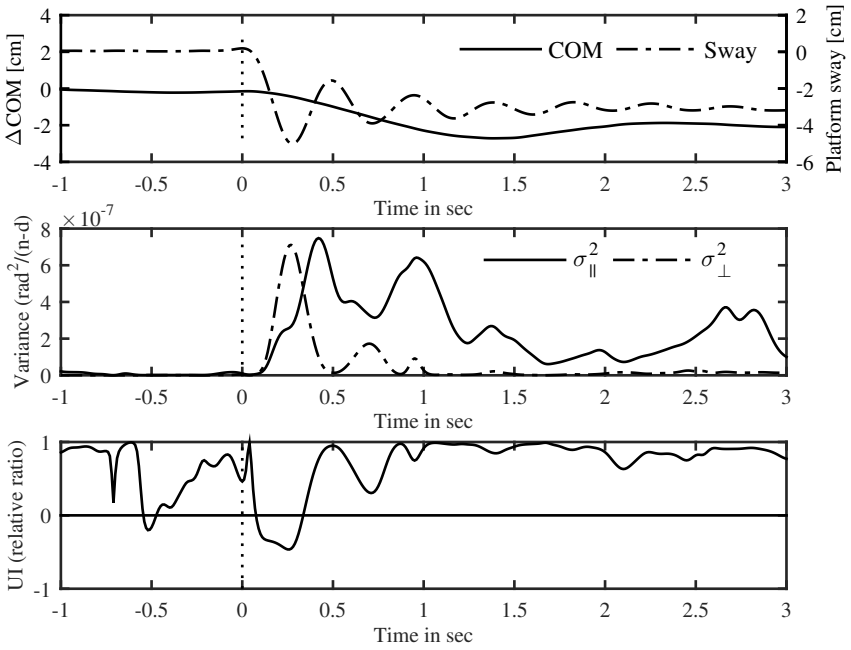

Figure 5.3: Typical motion data recorded during the postural task on the swaying platform: The dotted vertical lines indicate time point of platform release. Top panel shows centre of mass trajectory and actual platform sway trajectory. Middle panel shows normalised variance within and perpendicular to pre-perturbation joint configuration space. Lower panel shows relative ratio of variance.

for platform velocity and media-lateral sway, a three-dimensional motion sensor attached to the base of the platform recorded the platform acceleration at a sampling frequency of 1000 Hz (not part of the analysis). Finally, CP was recorded using the Zebris FDM-S pressure plate (sampling frequency 60 Hz, Zebris Medical GmbH, Isny im Allgaeu, Germany), which was centrally placed on top of the swaying platform. All final analysis algorithms were implemented and executed in Matlab^{TM} version 2014b for Mac (Mathworks Inc., Natick, MA, USA).

Centre of mass trajectory: The sagittal marker coordinates were used to calculate the joint angles of the foot (θ_F, with respect to the horizontal), the ankle angle between foot and shank (θ_A), knee angle between shank and thigh (θ_K), hip angle between thigh and pelvis (θ_H), lumbar angle between pelvis and trunk (θ_L) and neck angle between trunk and head(θ_N) [47]. Based on estimated segmental centres of mass (CM) and mass proportions, weighted sagittal plane CM (CM_x) location was computed for every frame [47]. A geometrical model relating CM_x to the joint configuration with origin at the toe was expressed through a trigonometric analysis

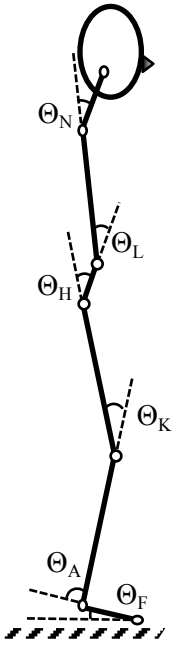

Figure 5.4: Marker configuration for kinematic data: Θ_N = Neck angle; Θ_L = Lumbar angle; Θ_H = Hip angle; Θ_K = Knee angle; Θ_A = Ankle angle; Θ_F = Foot angle; Marker positions (from head to toe): corner of the eye (orbital process of the zygomatic bone), mastoid process of temporal bone, acromion, anterior superior iliac spine, greater trochanter, lateral condyle of femur, lateral malleolus, calcaneal tuberosity, 1st metatarsal bone

(equation 5.1):

$$
\begin{aligned}
CM_x(x_{toe}, l_i, \theta_i) \;=\; & m_1 * (x_{toe} + d_1 * l_1 * cos(\theta_F)) + \\
& m_2 * (x_{toe} + l_1 * cos(\theta_F) + d_2 * l_2 * cos(\theta_F + \theta_A)) + \\
& m_3 * (x_{toe} + l_1 * cos(\theta_F) + l_2 * cos(\theta_F + \theta_A) + \\
& \quad d_3 * l_3 * cos(\theta_F + \theta_A + \theta_K)) + \\
& m_4 * (x_{toe} + l_1 * cos(\theta_F) + l_2 * cos(\theta_F + \theta_A) + \\
& \quad l_3 * cos(\theta_F + \theta_A + \theta_K) + d_4 * l_4 * cos(\theta_F + \theta_A + \theta_K + \theta_H)) + \\
& m_5 * (x_{toe} + l_1 * cos(\theta_F) + l_2 * cos(\theta_F + \theta_A) + \\
& \quad l_3 * cos(\theta_F + \theta_A + \theta_K) + l_4 * cos(\theta_F + \theta_A + \theta_K + \theta_H) + \\
& \quad d_5 * l_5 * cos(\theta_F + \theta_A + \theta_K + \theta_H + \theta_L)) + \\
& m_6 * (x_{toe} + l_1 * cos(\theta_F) + l_2 * cos(\theta_F + \theta_A) + \\
& \quad l_3 * cos(\theta_F + \theta_A + \theta_K) + l_4 * cos(\theta_F + \theta_A + \theta_K + \theta_H) + \\
& \quad l_5 * cos(\theta_F + \theta_A + \theta_K + \theta_H + \theta_L) + \\
& \quad d_6 * l_6 * cos(\theta_F + \theta_A + \theta_K + \theta_H + \theta_L + \theta_N))
\end{aligned}
\tag{5.1}
$$

where m_i is the i^{th} segment proportional mass expressed as percentage of total body mass, l_i

is the i^{th} segment's length, d_i is the distal distance from the the centre of mass of the i^{th} segment expressed as a percentage of its length, where $i = (1, ..., 6) = (foot, shank, thigh, pelvis, trunk, neck)$. The joint angles were primarily used to examine the relation of the elemental variables θ_i with the performance variable CM_x. Displacement of CM_x was calculated as the approximate integral of its trajectories.

Components of joint angle variability: For every recorded frame the variance of the control variables (i.e. joint angles) across the attempts can be partitioned into two components: parallel and orthogonal to the UCM (see below). The variance of the performance variable CM orthogonal to the UCM is usually smaller as compared to the variance parallel to it when standing in response to surface perturbation [28]. Both components of joint angle variability were computed to quantify the amount of variability causing unwanted change (non-motor equivalent) and the amount of variability returning the CM to its steady-state position (motor equivalent). The relative ratio of both components was reported to allow group-wise comparison. To obtain the variance of both components, the following steps were applied [28]:

1. Create geometric model (Eq. 1).

2. Use steady-state marker positions to compute a reference joint-configuration (mean joint configuration during 1 second prior to perturbation).

3. Compute the joint deviation vector (JDV) as the difference between the current joint-configuration and the reference joint-configuration for each segment $\bar{\theta_i}$ at every time-frame of the recording:

$$JDV = \begin{bmatrix} \theta_F - \bar{\theta_F} \\ \theta_A - \bar{\theta_A} \\ \theta_K - \bar{\theta_K} \\ \theta_H - \bar{\theta_H} \\ \theta_L - \bar{\theta_L} \\ \theta_N - \bar{\theta_N} \end{bmatrix} \tag{5.2}$$

4. Linearise the UCM to relate non-commensurate units with different numbers of degrees of freedom through the definition of the Jacobian matrix $J(\theta)$ and the computation of its null space around the reference configuration, $N(J)$.

$$0 = J(\bar{\theta}) * \epsilon_{n-d} = \begin{bmatrix} \frac{\delta CM_x}{\delta \theta_F} & \frac{\delta CM_x}{\delta \theta_A} & \frac{\delta CM_x}{\delta \theta_K} & \frac{\delta CM_x}{\delta \theta_H} & \frac{\delta CM_x}{\delta \theta_L} & \frac{\delta CM_x}{\delta \theta_N} \end{bmatrix} * \epsilon_{n-d} \tag{5.3}$$

$$N = \begin{bmatrix} \epsilon_{1F} & \epsilon_{2F} & \epsilon_{3F} & \epsilon_{4F} & \epsilon_{5F} \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ \epsilon_{1N} & \epsilon_{2N} & \epsilon_{3N} & \epsilon_{4N} & \epsilon_{5N} \end{bmatrix} \tag{5.4}$$

where ϵ_{n-d} are the basis vectors of the null space (n is the number of elemental variables and d is the number of dimensions of the performance variable) representing the linear subspace of all joint-configurations that leave the CM_x position unchanged.

5. Decomposition of the JDV projection into the null-space ($\theta_{||}$ and into its orthogonal space $\theta_{\perp}$:

$$\theta_{||} = \sum_{i=1}^{n-d} \Big(N(J)_i^T \cdot JDV\Big) N(J)_i \tag{5.5}$$

$$\theta_{\perp} = JDV - \theta_{||} \tag{5.6}$$

The computed scalar values represent the length of projection to quantify the consistency of the instantaneous joint configuration with the steady-state configuration.

6. Calculate variance normalised to the number of degrees of freedom $(n-d)$ and trial length (N):

$$\text{Motor equivalent: } \sigma_{||}^2 = \frac{\sum_{i=1}^{N} \theta_{||N}^2}{(n-d)N} \tag{5.7}$$

$$\text{Non-motor equivalent: } \sigma_{\perp}^2 = \frac{\sum_{i=1}^{N} \theta_{||N}^2}{dN} \tag{5.8}$$

7. Calculate relative variance as UCM-index (UI) [48]:

$$UI = \left(\frac{2\sigma_{||}^2}{\sigma_{||}^2 + \sigma_{\perp}^2}\right) - 1 \tag{5.9}$$

Centre of Pressure: Several CP quantifying parameters have been suggested in the literature [49]. For the purpose of this study, CP 95 % confidence-ellipse and standard-ellipse area (CEA and SEA) [50] were analysed as a measure of magnitude. Approximate entropy with dimensionality 2 and a tolerance of 0.2 times the standard deviation was analysed to quantify regularity of the time series, which has been reported to be more sensitive than magnitude alone [22].

Sample size

In the a-priori published trial protocol, an initial sample size of 10 patients per arm was nominated [29]. This was based on a recent study investigating the effects of a balance coordination training which reported a high effect size for functional status and pain of $d = 1.1$ and $d = 1.5$ respectively [54]. However, the study is not directly comparable to our procedures and according to a recent systematic review [26], studies of higher quality report considerably lower effect sizes (d=0.35). An updated sample size calculation accounting for 15% loss to follow-up, an assumed effect size of 0.35, an alpha value of 5/2% for directed hypothesis testing and a power of 80%, suggest a required sample size of 150 per arm. In light of the explorative approach and lack of directly comparable studies, the present pilot study aimed to recruit 25 patients with an expected drop-out rate of 15%.

Data analysis

Average values over five trials were used for kinematic variables. Due to non-normal distribution, heteroscedacity of variance and the small sample size, the parametric tests were deemed inappropriate for this study. Instead, robust methods for hypothesis testing with a between-within-design based on 20% trimmed means was conducted to analyse group and time effects [51]. Significance level was adjusted for multiple dependent variables based on the Bonferroni-Holms method (based on $\alpha = 0.05$) [52]. Similarly, overall change of primary outcomes for the entire study population was analysed with a one-way ANOVA and corrected for multiple comparisons. As a robust alternative to Cohen's d, explanatory measure of effect size were also estimated based on variation among the groups ($\hat{\xi}$). Cohen's d = 0.2, 0.5, and 0.8 (= small, medium, large effect) roughly correspond to $\hat{\xi} = 0.15$, 0.35, and 0.50, respectively [51]. Averaged values for both groups were statistically analysed in R-Studio v. 0.99.893 [53] and the statistical package 'WRS' v. 30 [51]. Intention-to-treat analyses was performed. Recorded outcome data of patients who dropped out after inclusion and randomisation were included in the final analysis (missing data reconstructed based on carry-forward method). Patients excluded before randomisation were not further analysed.

Results

From January 2015 to December 2015, 25 patients were recruited for the intervention trial. The last FU-assessment was recorded in January 2016. Following BL assessment, three patients dropped out prior to randomisation and were not included in the analyses (Figure 5.1). One dropout patient withdrew due to limited time available to participate in the entire trial. One patient had to be excluded after BL due to language and compliance difficulties during assessment and it was deemed best to terminate the participation at this point. Finally, another patient was excluded because a closer clinical examination after referral revealed obvious signs of nerve

root compression with sensorimotor deficits in lower extremities. 22 patients (11 females, mean age = 55 years (32 to 75), mean pain at BL = 22.5% ($CI_{95\%}$ = 17.4 *to* 27.6%), mean ODI at BL = 18.1% ($CI_{95\%}$ = 13.8 *to* 22.5%)) were included for intention-to-treat analysis (11 per arm). One patient in the experimental intervention group failed to appear to BL and FU measurements but completed all the therapies and immediate pre- and post-intervention tests (T0 and T1). In four cases, patients only attended 8 of the 9 therapies due to sickness not related to the study. Hence, 81.1% of patients attended all regular PT sessions. In 72.7% (N = 16), all documentation sheets were flawlessly filed and therapies conducted according to protocol. In one case of the SMT group, the patient failed to attend the additional therapy once. In two cases of the SLIT control group, patients failed to attend the additional therapy once. Treatment was not modified during the study and no particular change in lifestyle and activity levels were reported by the patients. Analyses of therapy documentations showed comparable doses and frequency of active and passive treatments in both groups (i.e. mobilisation, strengthening, and passive manual therapy).

Primary outcome measures

Functional Status

Overall, ODI scores improved significantly from BL to T1 and T2 ($F_t(2.4; 31.7) = 6.5$, $p < 0.01$). Clinical relevant improvement from BL to T1 ($\geq 8\%$) was observed in eight participants, two in the SLIT- and six in the SMT-group. At T2, 10 patients of the SMT group reported clinical relevant improvement since BL compared to only two in the control group. After 4.5 weeks, the average reduction in the SMT group was 6.6% ($CI_{95\%} = -6.7\%$ *to* 19.8%) and 5.1% ($CI_{95\%} = -10.1\%$ *to* 20.8%) in the control group. Both groups improved from BL to four-weeks follow-up (FU, see Table 5.2 and Figure 5.5), but only the SMT-group to a significant extent with a within change of 11.5% ($CI_{95\%} = 5.3\%$ *to* 17.7%, $t = 7.19$, $p < 0.001$). However, the two-way ANOVA based on trimmed means showed no significant group and time interaction ($Q_{interaction} = 3.30$, $p = 0.07$). The explanatory effect size for the group effect was $\hat{\xi} = 0.11$ and for time effects from BL to T1 and FU $\hat{\xi} = 0.45$ and $\hat{\xi} = 0.62$, respectively. Interaction effects from BL to T1 and FU were $\hat{\xi} = 0.16$ and $\hat{\xi} = 0.45$, respectively.

Self-reported pain

Overall, VAS scores also improved significantly from BL to T1 and T2 ($F_t(2.4; 31.1) = 4.0$, $p < 0.02$). Clinical relevant improvement from BL to T1 ($\geq 13\%$) was observed in nine participants, four in the SLIT- and five in the SMT-group. At T2, eight participants improved by more than 13%, four in each group. From BL to T1, VAS-pain scores decreased by 6.6% ($CI_{95\%} = -5.0\%$ *to* 18.2%) in the control group and by 5.6% ($CI_{95\%} = -16.8$ *to* 28.2%) in the SMT group. Accordingly, there was no significant group, time or interaction effect observed ($Q_{between} = 0.63$,

Table 5.2: Main results of primary and secondary outcomes at 4 MEs.

	Control T-Mean (CI_L - CI_U)	Experimental T-Mean (CI_L-CI_U)	$\delta(CI_L - CIU)$	t	p
Primary outcomes					
ODI [%]					
BL	16.00 (4.76 - 27.24)	19.71 (14.43 - 25.00)	3.71 (-0.19 - 0.11)	-0.75	0.47
T0	17.71 (4.09 - 31.33)	16.29 (8.90 - 23.67)	1.43 (-0.17 - 0.20)	0.23	0.82
T1	10.86 (5.72 - 15.99)	13.14 (4.91 - 21.38)	2.29 (-0.14 - 0.09)	-0.59	0.57
FU	12.29 (7.12 - 17.45)	8.23 (2.28 - 14.18)*	4.06 (-0.05 - 0.13)	1.30	0.22
VAS [%]					
BL	19.89 (12.08 - 27.69)	24.76 (17.24 - 32.27)	4.87 (-0.17 - 0.08)	-1.13	0.28
T0	22.23 (9.50 - 34.96)	25.13 (18.67 - 31.58)	2.90 (-0.20 - 0.14)	-0.51	0.62
T1	13.71 (3.88 - 23.55)	18.79 (6.25 - 31.32)	5.07 (-0.24 - 0.13)	-0.80	0.44
FU	15.47 (8.76 - 22.19)	15.59 (3.31 - 27.86)	0.11 (-0.17 - 0.17)	-0.02	0.98
Secondary outcomes					
CM [cm]					
BL	1.92 (1.47 - 2.38)	2.28 (1.79 - 2.77)	0.35 (-1.12 - 0.41)	-1.34	0.21
T0	1.95 (1.39 - 2.52)	2.44 (1.76 - 3.12)	0.48 (-1.50 - 0.53)	-1.38	0.19
T1	1.82 (1.52 - 2.12)	2.19 (1.60 - 2.78)	0.37 (-1.18 - 0.43)	-1.41	0.19
FU	1.78 (1.49 - 2.08)	2.17 (1.68 - 2.66)	0.39 (-1.06 - 0.28)	-1.73	0.12
UI [ratio]					
BL	0.33 (0.28 - 0.39)	0.51 (0.38 - 0.65)	0.18 (-0.36 - 0.00)	-3.14	0.01†
T0	0.34 (0.23 - 0.45)	0.48 (0.33 - 0.64)	0.14 (-0.36 - 0.07)	-1.97	0.08
T1	0.39 (0.25 - 0.53)	0.48 (0.41 - 0.54)	0.09 (-0.27 - 0.10)	-1.45	0.18
FU	0.34 (0.20 - 0.49)	0.48 (0.42 - 0.54)	0.14 (-0.33 - 0.06)	-2.22	0.06
CP [cm]					
BL	11.67 (7.71 - 15.63)	14.53 (8.72 - 20.34)	2.86 (-11.08 - 5.37)	-1.03	0.33
T0	8.13 (3.80 - 12.46)	11.89 (6.20 - 17.58)	3.76 (-12.05 - 4.52)	-1.33	0.21
T1	7.16 (5.04 - 9.29)	11.93 (5.49 - 18.37)	4.76 (-13.39 - 3.86)	-1.77	0.12
FU	9.11 (8.02 - 10.20)	10.11 (7.27 - 12.94)	1.00 (-4.81 - 2.81)	-0.83	0.43
ApEn [ratio]					
BL	0.24 (0.22 - 0.26)	0.25 (0.23 - 0.26)	0.01 (-0.04 - 0.02)	-1.20	0.25
T0	0.23 (0.19 - 0.27)	0.24 (0.20 - 0.29)	0.01 (-0.08 - 0.06)	-0.35	0.73
T1	0.24 (0.21 - 0.26)	0.23 (0.20 - 0.26)	0.01 (-0.04 - 0.05)	0.48	0.64
FU	0.24 (0.19 - 0.28)	0.28 (0.24 - 0.32)	0.04 (-0.11 - 0.03)	-1.72	0.11

Trimmed means (T-mean, 20%) of primary and secondary outcomes at baseline (BL), pre- and post intervention (T0 and T1), and four weeks follow-up (FU). δ= mean difference between groups, CI_L and CI_U = upper and lower 95% confidence interval, t=robust t-statistic of between difference, p=p-value of between-difference. *Significant within-change since BL ($p < 0.001$). †=unadjusted significance for between difference.

$p_{between} = 0.44$; $Q_{within} = 1.92$, $p_{within} = 0.19$; $Q_{interaction} = 0.84$, $p_{interaction} = 0.51$). The explanatory effect size for the group effect was $\hat{\xi} = 0.20$ and for time effects from BL to T1 and FU $\hat{\xi} = 0.32$ and $\hat{\xi} = 0.36$, respectively. Interaction effects from BL to T1 and FU were $\hat{\xi} = 0.03$ and $\hat{\xi} = 0.14$, respectively.

Secondary outcome measures

Centre of mass and uncontrolled manifold index

The kinematic data showed virtually no change over time and remained stable in both groups. The amount of CM trajectory after both interventions was reduced by 8.3 mm in the SMT group and 1.1 mm in the control group. However, there was large variance in both groups with $CI_{95\%}$ ranging from $-55.1mm$ to $71.7mm$ and from $-84.1mm$ to $86.5mm$, respectively ($Q_{between} = 3.34$, $p_{between} = 0.10$; $Q_{within} = 0.86$, $p_{within} = 0.49$; $Q_{interaction} = 0.05$, $p_{interaction} = 0.98$). Although the variance index UI did not change over time in either of the groups, only the SMT group showed significant reduction of motor equivalent variance within the stable sub-space at FU (p = 0.03), but no change within the orthogonal sub-space. However, when corrected for family wise error and baseline imbalance, the main interaction effect of variance within the stable sub-space was non-significant ($Q_{interaction} = 1.63$, $p_{interaction} = 0.27$). The explanatory effect size for the CM group effect was $\hat{\xi} = 0.45$, primarily caused by the baseline imbalance. For CM time effects, effect size from BL to T1 and FU were $\hat{\xi} = 0.32$ and $\hat{\xi} = 0.36$, respectively. Interaction effects from BL to T1 and FU were $\hat{\xi} = 0.03$ and $\hat{\xi} = 0.14$, respectively. The explanatory effect size for the UI group effect was $\hat{\xi} = 0.65$, also caused by the baseline imbalance. For CM time effects, effect size from BL to T1 and FU were $\hat{\xi} = 0.32$ and $\hat{\xi} = 0.36$, respectively. Interaction effects from BL to T1 and FU were $\hat{\xi} = 0.03$ and $\hat{\xi} = 0.14$, respectively.

Center of pressure derived data

Whereas the structure (i.e. predictability) of the CP, approximate entropy, remained unchanged throughout all measurement events (ME), the magnitude of CP displacement slightly reduced in both groups ($Q_{between} = 2.54$, $p_{between} = 0.15$; $Q_{within} = 3.17$, $p_{within} = 0.08$; $Q_{interaction} = 1.19$, $p_{interaction} = 0.37$). The explanatory effect size for the CP group effect was $\hat{\xi} = 0.41$ and for time effects from BL to T1 and FU $\hat{\xi} = 0.39$ and $\hat{\xi} = 0.51$, respectively. Interaction effects from BL to T1 and FU were $\hat{\xi} = 0.21$ and $\hat{\xi} = 0.09$, respectively.

Safety

All patients tolerated the SMT program and no serious adverse events occurred. All patients rated trial procedures as tolerable, but in one patient, for no explainable reason, clinically relevant worsening of functional status by 10% on the ODI scale was observed.

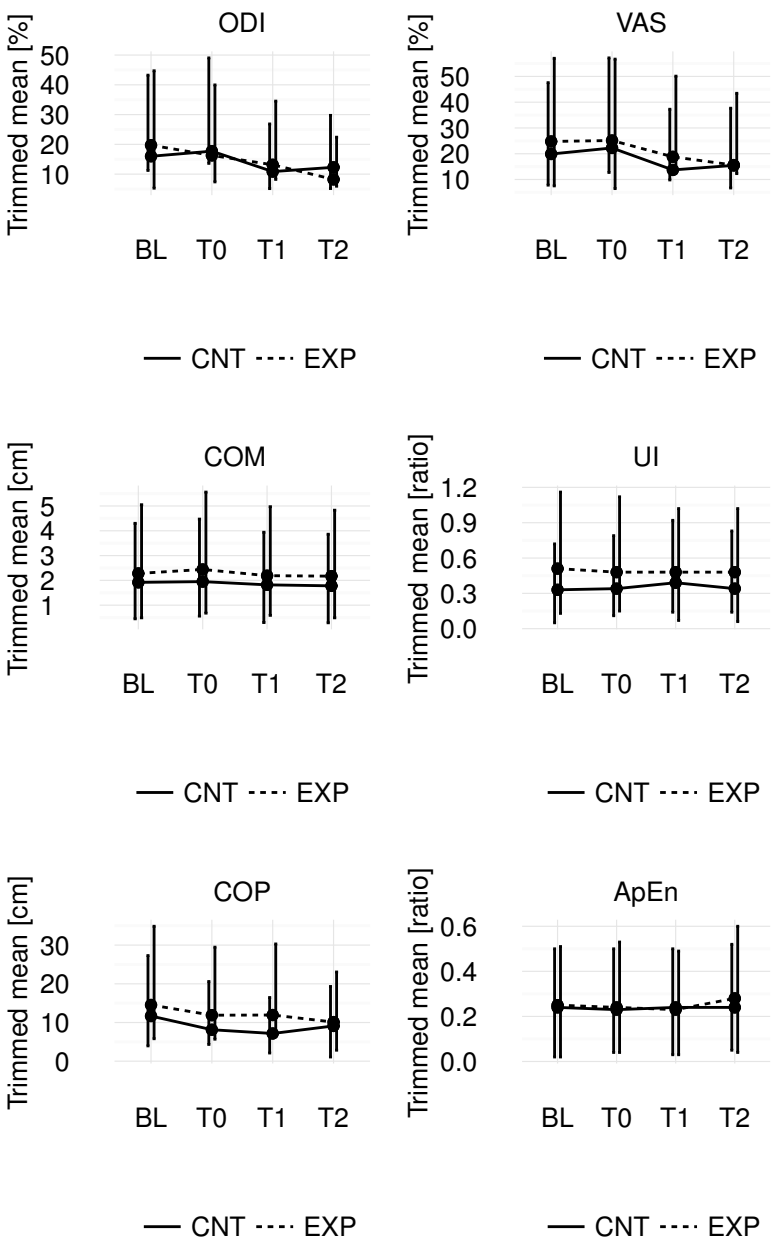

Figure 5.5: Development of primary and secondary outcomes: CNT=control group (SLIT), EXP=experimental group (SMT), ODI=Oswestry Disability Index, VAS=Visual Analogue Scale of Pain, CM=centre of mass, CP=centre of pressure, UI=Uncontrolled Manifold Index, ApEn=approximate entropy

Discussion

This randomised clinical pilot trial examined the effects of SMT as part of standard physiotherapy programs during CNLBP rehabilitation compared to sub-effective low intensity endurance exercise. The series of treatments resulted in a substantial reduction in functional impairment

and self-reported pain, particularly at four-weeks follow up in the SMT group. However, no significant group-by-time effects on either of the primary or secondary parameters were observed, suggesting that, on average, attending additional low doses of SMT units on a regular base does not have any significant benefits when compared to low levels of added general activity. Both groups showed no change of motor reaction to the perturbation task submitted to the patients during the postural control assessment.

This is the first randomised trial evaluating the effects of a SMT with equal group size, a standardised and theory-based training program, and a comparable active control group with equal time spent with therapists. Other trials with similar aims were summarised in a recent systematic review [26]. Although most trials showed promising effects, the low quality of the cumulated findings prevented final conclusions and clear recommendations [26]. Some of the included trials claim that SMT allows patients to regain muscular balance, which is supposed to be partly responsible for pain alleviation and improved neuromuscular coordination [54]. However, in that particular study doses and frequency was higher than in the present study with five 40 minute treatments per week during four weeks compared to passive controls. Hence, the observed effects cannot be conclusive, as they may be non-specific rather than attributed to SMT alone. Other research in elderly populations has suggested that SMT may be beneficial as part of exercise programs to improve balance and reduce risk of falls, but not to a greater extent than usual exercise [55].

Similarly, in a narrative review on the topic, Lederman points out that there seems to be no specific proprioceptive exercise [56]. When compared to other exercise, both approaches are likely to be equally effective [56]. This is in line with other studies reporting that individuals without CNLBP, seem to spend significantly more time with moderate activity, e.g. climbing more steps on a daily base, than CNLBP patients [57]. Persistence of pain may, therefore, be related to the often observed withdrawal from physical activity with no specific effect on the sensorimotor system [6].

In an effort to standardise SMT, several researchers have put together three principles that must be adhered if any effect from SMT could be expected [36, 56, 58, 59]. First, the level of instability must be adjustable and incremental over time. The participant must be able to control the task to complete the exercise properly, but still be challenged when progressing his or her skills [12, 36]. Second, the participant must be able to respond to the instability, i.e. there must be closed-loop control system in which feedback is compared to an intended goal [12, 36]. Finally, the exercise at hand must include a secondary task (i.e. dual task) which is separated from the functional stability task (e.g. juggling a ball or cognitive challenge) once the participant has advanced to a certain level in order to centralise the acquired skills [36]. The investigated SMT program adheres these principles, but it should be noted that due to lacking recommendations of doses and frequency of SMT, the chosen duration was arbitrary and might be too little to provoke any training effects. Although the doses and frequency chosen was similar to previous studies with active comparator groups, e.g. three times 15 minutes a week for five weeks in a

study on the effects on neck pain [60], the relative amount of added experimental therapy might have been too short with the main effect of the treatment owed to the actual treatments applied during standard PT. SMT targets postural muscles vastly consisting of aerobic type I muscle fibres (e.g. erector spinae). These muscles are inherently fatigue resistant and would likely require high volume and frequency to provoke any training effect [59]. Moreover, the common problem of too small sample sizes in CNLBP trial and the high heterogeneity of symptoms and functional status should be considered. The population sample in the present study presented with moderate to low pain levels and generally reported to be leading an active lifestyle. The putative training effect of SMT is likely to be more pronounced in patients with lower levels of activity and higher pain levels and functional impairment.

Whether the UCM analysis is an appropriate measure to evaluate movement variations in pain affected people is certainly a point of discussion and should be investigated in more detail, possibly with other movement tasks that have shown to deviate in CNLBP patients. One study has shown reduced task-specific variability during a sit-to-stand task in young CNLBP patients with low pain levels [61] while another study found increased task-specific variability during a postural task on a labile surface, indicating more segmental variation to achieve the same goal [62]. Moreover, the CM is a theoretical construct and may not be the relevant performance variable. However, all the studies conducted to test this hypothesis have confirmed the importance of CM control during postural tasks [41, 28]. Despite the number of trials produced on the topic, the sensitivity of the UI has not been investigated yet and our trial might have been underpowered to show the expected effects, although other trials with repeated measures were of similar size [43].

Despite attempts of blinding the patients to the experimental condition through a quasi-sham intervention, it did not take much to learn about the experimental condition. Thus, the intervention could not be entirely blinded to the participants, for which reason non-specific effects contributing to the minor differences observed cannot be out-ruled. Further, leisure activities of the patients could not be controlled or restricted during the study. However, no particular change in lifestyle habits was reported from any patients. Finally, the sample size was small with a large heterogeneity concerning pain levels and postural control which limits the generalisability of the trial's findings.

Nevertheless, the presented pilot study shows a positive trend with high interactions effect sizes for the improvement of functional status in CNLBP after receiving added SMT in standard physiotherapy programs, albeit without any change in movement behaviour. The mechanisms behind the role of SMT advocated by its proponents need to be addressed in basic research before further clinical trials on the effect of motor control are warranted to understand which parameters should be recorded and who would benefit, if at all, from sensory variability of this sort. Higher firing rates in afferent receptors may not necessarily cause peripheral change or central motor re-learning [58, 36]. To provide evidence of the trainability of the sensorimotor system through balance training, it must be shown that acuity of sensory receptors and the signal

conversion to and within the CNS can be enhanced [36]. More findings are needed showing in humans that the functional instability of joints can be addressed with SMT [58, 36, 62]. Once the latter questions are resolved, a large-scale study would be warranted to investigate the effects of SMT on functional status and to define the minimal training recommendations.

Conclusion

In patients with moderate CNLBP, physiotherapy with added SMT or SLIT improved impaired functioning with no significant group difference. Short-term effects on pain and function seem to be similar for either kind of added activity, but the findings suggest potential benefits of SMT for long-term functional status. No improvement in terms of postural response to platform perturbation was observed. Multi-segmental postural control and centre of pressure remained unchanged throughout the trial. Possible effects on postural parameters of higher doses and frequencies of SMT cannot be out-ruled. The findings cannot be generalised to population with higher pain levels, who may be more responsive to the intervention.

Competing interests

The authors declare that they have no competing interests.

Author's contributions

MM, EB, BW, and CS developed the research question under MM's lead. MM developed the study design and measurement setup while EB, BW, and CS acted as methodological councils. MM proposed the study protocol, which was edited and improved by EB, BW, and CS. MM produced an early version of this paper. EB, BW, and CS substantially revised the paper to bring it to its current form.

Acknowledgements

The authors wish to extend their gratitude to the therapists involved in the intervention of this trial. Specifically Zorica Suica, Sabrina Naegelin, Pamela Spengler, Michaela Zimmermann, Astrid Stern, Christian Seibt, and Felix Mauch have provided guidance for important clinical aspects to the trial's intervention. Dr. Christopher M′ussig was strongly involved during the screening phase and clinical examination of all patients. The authors also wish to thank Vivien Gnehm and Maria Emmert, who contributed to the assessments during their student project. The contributions to improve data acquisition from Dr Rolf van den Langenberg, Michelle Anliker, and Michael Preiswerk significantly increased the reliability of the motion tracking setup and should also be acknowledged. Finally, the critical remarks of Prof. N. Wenderoth have

helped to produce the final procedures implemented for this trial. ProPhysics AG generously provided measurement equipment during the pilot-phase and counselling for the setup, for which the authors would like to thank Yve Hess and Erwin Schweizer. The study is partially funded by a grant from the cantonal department of health and social services of the Canton of Argovia, Switzerland, without which the interventions could not have been performed to this extent.

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CHAPTER 6

General Discussion

Main findings

Sensorimotor training as part of physiotherapy in CNLBP rehabilitation

In the first part of this thesis, the current evidence for the use of sensorimotor training (SMT) in rehabilitation of patients with chronic neck- and back pain was summarised. The initial idea of the systematic review was to search the literature for best practice in SMT, i.e. which SMT doses and materials can currently be recommended for musculoskeletal pain rehabilitation. It soon became clear, that the available literature does not allow conclusive recommendations on the use of SMT modes. We had to step back a few paces and ask a more fundamental question: Does any evidence support the use of SMT in musculoskeletal pain rehabilitation at all? With a widespread and methodologically solid systematic literature review based on current guidelines, major health databases were searched for all pieces of potential evidence. Despite these efforts, we could not ascertain a clear answer to that question. However, as it goes, there is no evidence of absence. Although we found no convincing result to confirm the benefits of SMT, we did not find any proof of the opposite either.

Most interventions with proprioceptive elements (i.e. SMT) did report some reduction in pain and improvement of functional status, but the methodological approaches did not allow us to causally connect the reported effects to the experimental interventions. With multiple low-quality RCTs reporting conflicting findings on the effectiveness of SMT on pain and functional status, our qualitative analysis could not provide any conclusive recommendations. We found that there is generally only low quality evidence that the SMT applied alone is more effective than passive treatments or even placebos. Only when incorporated with multimodal treatment methods, i.e. as part of physiotherapy or added to other physical exercise, low quality evidence suggests certain benefits in short- and long-term outcomes of pain and function. Interestingly, our findings also showed that there is low quality evidence for the superiority of educational and behaviour approaches over SMT in long-term rehabilitation of chronic non-specific low back pain (CNLBP).

With this systematic review (chapter 2), we identified a major gap in the literature of exercise therapies and, in response, initiated the SeMoPoP trial (**Se**nsori**Mo**tor Training, **Po**stural Control, and **P**ain). In cooperation with therapists, physicians and movement scientists, a study protocol for the evaluation of SMT in a clinical setting was outlined. The produced study protocol (chapter 3) was published soon after and led to the intervention trial reported in chapter 5. It was the first RCT evaluating the effects of SMT with equal group sizes, a standardised and theory-based training program, and a comparable active control group with equal time spent with therapists. Despite significant improvement in functional status after SMT, overall findings of this study suggested that, in patients with moderate CNLBP, short bouts of added SMT as part of prescribed physiotherapy provides no added benefit for pain reduction or functional improvement. But the findings did suggest potential benefits of SMT for long-term

functional status, as interaction effect size was large. In terms of postural control it was found that multi-segmental variance and centre of pressure outcomes remained unchanged throughout the trial.

There is large interest on the topic of SMT in pain management with countless research being carried out globally. By and large, our findings are congruent with recent publications with comparable designs. In a systematic review on exercise interventions in chronic neck pain by O'Riordan et al., it was carefully recommended that elements of proprioceptive exercises within a multimodal approach could "produce favourable outcomes" [1] (page 781). The included studies were conducted between 2000 and 2012 and were only included if comparators received some form of active treatment too. Although they included 16 studies for their meta-analysis, the authors had to point out that only two studies had investigated SMT with only one of them suggesting beneficial effects. Two reviews of the Cochrane Database were conducted on the effects of exercise with SMT elements in hamstring injury prevention [2] and, more recently, neck pain and function [3]. Goldman et al. [2] found that the summary of evidence in the literature from 1980 to 2008 does not show any statistically significant effect for the prevention of hamstring injuries through proprioceptive exercise. In line with our findings, Gross et al. [3] found only very low evidence that suggests SMT could improve pain and function. Macedo et al. [4] published a systematic review with similar exercise methods, termed motor control exercise, in a population with CNLBP and suggests that motor control exercises may be beneficial when added to another therapy but are no more effective than other forms of exercise.

Taking a closer look at individual studies, that have not been included in any systematic review, we often find surprisingly optimistic results. For instance, Eils et al. [5] recommend SMT for ankle instability rehabilitation, although the results show no consistent improvement, there was no active control group, and the sample size differed significantly. In the prevention of falls in the elderly population, Alfieri et al. [6] published a RCT in 2012, in which SMT exercise resulted in significant improvement of postural control outcomes. But the authors had to conclude that due to absent interaction effects, the improvement may be non-specific rather than caused by SMT.

The mentioned literature and our findings presented in this thesis provide collected evidence that exercise with SMT elements can be beneficial as part of a multimodal therapy approach, particularly in the long-term improvement of functional status. But it is yet to be shown that the observed effects truly come from the experimentally added SMT alone and is not caused by general activity and other exercise, which seem to have equal effects. In this sense, I would like to quote Eyal Lederman from his book on Neuromuscular Rehabilitation (page 48), who pragmatically claims that "there is no specific proprioceptive exercise. All activities are likely to be equally effective" [7].

Uncontrolled manifold analysis of postural control in patients with CNLBP

The second main goal of this project was to investigate and disseminate the potentials and limitations of non-linear assessments in rehabilitative settings. Briefly mentioned within the study protocol (chapter 3), the main cross-sectional study was designed as part of the longitudinal study (chapters 4 and 5). Exploiting the baseline measurement of the RCT, a healthy control group was recruited and measured once for comparison. It was the first study that investigated multi-segmental kinetics in patients with CNLBP and conducted follow-up assessment after SMT interventions. We found that patients with CNLBP showed significantly different postural strategies than the pain-free comparator group. The hypothesis, that both groups would show no difference in centre of pressure (CP) and centre of mass (CM) trajectory was accepted. The second hypothesis, that patients with CNLBP would have, on average, a lower ratio of motor equivalence to non-motor equivalence, had to be rejected.

The baseline data comparison with pain-free controls, showed that both groups were able to maintain a stable CM position while standing on a labile platform. Joint angles quickly returned to steady-state configuration in both groups which was reflected by significantly higher variance within the uncontrolled manifold (motor equivalence) compared to the orthogonal subspace (non-motor equivalence). This is consistent with previous findings describing control of undesirable deviation of task goals rather than control of each segment to reach that goal [8, 9, 10]. A notably higher degree of motor equivalent variance was observed in the CNLBP group when compared to the pain-free group. Although not statistically significant, the medium sized effect of d=0.31 underlines the additional effort observed in the CNLBP group to maintain a desirable CM position. Significantly more hip-segment movement was observed in the CNLBP group whereas none of the CP measures were able to identify such differences. This is in line with the most recent meta-analysis on CP in CNLBP [11]: unless sensory provocation is applied, e.g. through proprioceptive spindle vibration, CNLBP patients do not present with significantly greater CP trajectories.

Changed motor control patterns in postural tasks has been described elsewhere. In 2008 [12] and again in 2010 [13], Brumagne and Claeys showed how patients with recurrent LBP seem to be less adaptive to different postural conditions when compared to pain-free controls. Whereas participants from the control group changed their postural strategies, i.e. using various joint segment configurations, the LBP group was reported to use the same rigid strategy for every condition. This was investigated by means of relative proprioceptive weighting, a method which allows attribution of control strategies to particular segments [13]. The results suggested, that patients with CNLBP were less capable of multi-segmental adaptability in unstable conditions. The authors concluded, that the predominant compensation of the unstable support surface by ankle variation, would cause undue spinal loading and contribute to pain recurrences. In a follow-up study, published in 2015, Claeys et al. [14] showed that the previously described, less adaptable postural strategy increased the risk for developing or having recurrences of mild

LBP within two years more than threefold [14]. Similarly, applying the UCM approach, Tajali et al. [9] found significantly lower values of motor equivalent variance in a LBP group during a sit-to-stand task. The group concluded that LBP patients adopted a more rigid strategy during the dynamic phase of the task.

These findings may seem at odds with our discoveries. However, in light of another study on dynamical non-linear analysis of postural control outside CNLBP research, a crucial discrepancy of the studies may be the pain duration of the patients. Black et al. [15] used the UCM analyses to show how children with Down Syndrome employ a different motor control strategy when walking on a treadmill. While both groups were able to stabilise the CM sufficiently, children with Down Syndrome required more variability from the task space (motor equivalent), relying on a larger selection of solutions and thereby actually increasing complexity, rather than decreasing it. Reduced variability in young patients with CNLBP and relatively short durations of chronicity, observed in Brumagne et al. [12], Claeys et al. [13], and Tajali et al. [9], can be explained with well described protective compensation methods in early stages of pain occurrence (e.g. rigid muscle activity with low flexibility) [16, 17]. On the other hand, long-term moderate pain may lead to increased variance, indicative of new postural control strategies adopted to cope with dynamic environments. This does not mean that chronic conditions lead to more stable reactions, but the natural tendency to more efficient movement required more sets of segmental configurations to achieve the same stability as unaffected people. Too much uncontrolled variance may lead to excessive motion outside the physiological limits of passive structures which stabilise the spine [18], thereby contributing to pain sustenance. This would coincide with the observed increase in total angle excursion with higher pain states presented in our article (chapter 4). This may also explain why these consolidated movement strategies did not change within such a short duration of the intervention (chapter 5), where all postural control parameters remained virtually unchanged.

Thus, rather than contradicting previous findings, the results of our studies extend these and suggest possible long-term adaptations of postural control with increased variability to increase complexity and cope with new sets of demands. Redundancy allows reactive movements in unexpected situations which provides flexible and stable motor actions (adaptive flexibility through redundancy) [19]. I would like to end this section, again, with a fitting quote by N.N. Taleb on 'Things that Gain from Disorder' (page 44-45): "Layers of redundancy are the central risk management property of natural systems [...]. Redundancy is ambiguous because it seems like a waste if nothing unusual happens. Except that something unusual happens - usually."

Limitations and methodological considerations

Methodological and statistical heterogeneity of the literature included in the systematic review allow only limited interpretation of the qualitative findings and prevented a meta-analysis. This was partly due to the scarcity of specific SMT studies in patients with CNLBP, but also because

of insufficient data reported in the studies. Relevant outcomes were not sufficiently described suggesting high risk of selective reporting bias and low transparency. Furthermore, although all relevant databases were searched, the review may have failed to include all studies investigating the effect of SMT in CNLBP, because of the arbitrary use of expressions (cybernetic exercise, SMT, etc.). There is no consistent term for SMT and it may be argued that motor control exercises [20] and perceptive rehabilitation [21] should not have been included in this SR, or, conversely, Saner et al., who assessed movement control exercises in a RCT [22], should have been included.

Study sample

Heterogeneity

As mentioned earlier, a common problem of CNLBP intervention trials with small sample size is the high heterogeneity of symptoms and functional status often observed within and between participants. Not only does severeness of symptoms change on a daily base with sudden unexplainable flareups, but the multifactorial causes of CNLBP may be weighted highly inconsistently among individuals. Pathogenic potentials that may lead to pain include subtle congenital anomalies, functional change (i.e. posture), age, gender, climate, occupational risks and occupational attitude, mental and physical stress, repetitive sub-lesions through sports and leisure activities, social situation, and more. Accordingly, recent findings suggest subgrouping of patients for stratified care to target treatments according to key characteristics. This is supposed to maximise treatment effects, reduce harm, and increase efficiency of health care systems [24]. There is no doubt about the cost-effectiveness of the stratifications in primary care, which has been demonstrated previously [24]. It prevents over treatment of patients who have high potential of recovery and quickly re-integrates them into their social environment [24]. However, in patients with existing CNLBP, the effects of stratified care have not been as convincing so far [25, 26]. Based on this, and on previously conducted sample size calculation, our sample size was deemed sufficient and feasible. The moderate pain levels reported by the included patients limits the generalisability of the trial's findings to pain population with more severe symptoms, but reflects the clinical picture of many chronic pain patients who experience sudden flareups rather than constant excruciating pain.

For the cross-sectional study, it may be argued that the significant age difference between the groups may have been responsible for the observed difference in outcome measures. However, only a relatively small effect of age on these postural parameters has been described elsewhere [27]. Also, the analysis was repeated without age-specific outliers and no notable difference in the results was found.

Outcome measures

Primary outcomes

Pain is a complex phenomenon, which, for practical reasons, is often recorded with subjective outcome measures [28] and is not always related to functional impairment [29]. However, from both a patient's and a clinicians perspective, the most important outcome is how current pain status is perceived by the patients. The VAS for pain and the Oswestry Disability Index provide simple and minimally intrusive means of pain assessment and have both shown to be valid and reliable tools to screen and monitor patients with CNLBP [30].

Secondary outcomes

It seems clear that when we are in pain, we move differently. We use nociceptive feedback to react to potential danger or tissue damage. Under pain, movement are adapted towards reduced pain. Changes may occur in amplitude of movements (i.e. reduced range of motion), reduced speed of movement, or prevent contact during movements. All of these adaptations may be analysed in different ways (kinematic assessment of speed, kinetic assessment of torque, electrophysiological assessment of recruitment patterns). These facts stress the importance of task specificity of physiological functions and necessity to design the task of study appropriately. In our study we chose to assess postural control while standing on both legs on a slightly perturbed platform. This is in contrast to other postural tasks, where either the perturbation is subjected to the patient via an automated platform, or a sit-to-stand task is performed. Possibly the perturbation caused by the swaying platform in our study was insufficient to provoke abnormal responses. We were of the opinion that any increase in sway or change to more complex movement tasks would have failed to represent a functional component of daily activity and impaired standardisation.

Further, the CM is a theoretical construct and may not be the relevant performance variable to observe during a postural task. Although all studies conducted on the issue so far have confirmed the importance of CM control during postural tasks [31, 8], it may well be that other performance variables, such as the head position, play a greater role in patients with CNLBP. Whether the UCM analysis is an appropriate measure to evaluate movement variations in pain affected people is certainly a point of discussion and should be investigated in more detail, possibly with other movement tasks that have shown to deviate in CNLBP patients. Despite the number of trials produced on the topic, the sensitivity of the UCM-index has not been investigated yet and our trial might have been underpowered to show the expected effects. Only one other trials with repeated measures was conducted so far in children with Down Syndrome where movement variability is inherently bigger and change easier to identify [15].

The issue of proprioception was insufficiently addressed in this dissertation. As described within the study protocol in chapter 3, the assessment of joint repositioning sense was also part of our cross-sectional analysis. This satellite project was conducted by one of the students I

supervised during the trial [32]. The results are not reported within this dissertation as they were not concluded at the time of compilation and are not part of my original work.

Measurement setup and equipment

One major limitation of this trial was the usage of novel measurement device possibly deviating from gold-standards. This limits comparability with other studies that use more sophisticated 3D marker tracking systems, such as Vicon. In an attempt to assess the comparability with gold-standard systems, a pre-trial pilot test was conducted with simple movement tasks performed on both systems. Furthermore, geometrical objects with fixed and known metrics were recorded prior to assessments to calibrate the recordings. Although the results were comparable and accuracy estimated at 1-2mm, these experiments must be repeated in a more systematic way to allow final conclusions on the measurement errors of the device. Marker tracking also poses the inherent discrepancy from actual joint angles and anatomical reference positions caused by soft tissue deformability and marker positioning accuracy [33, 34]. Using only 2D analysis in the sagittal plane has also been reported to increase the possibilities of errors [34]. However, in cases of movement limited predominantly to one plane results have been shown to be comparable to 3D analysis [34].

Intervention

The experimental intervention of SMT is comprehensively described and all therapists were trained in its standardised instructions. Moreover, it is theory-based and complies with all current principles known for SMT. Its limitation is the lack of knowledge of doses and frequency. There is no clear definition on how long and how often it should be used. Practically, therapists usually apply it for a couple of minutes within the weekly therapy sessions or until sensorimotor depletion is observed, i.e. to the point where the exercise is no longer deemed to be performed in satisfactory quality. The duration was set to 15 minutes based on the experience of the involved therapists, not on evidence based recommendations. It may seem as if the duration of just 15 minutes is too little, however, considering that patients usually only spend 30 minutes with therapists, this is a rather high relative duration of the total time spent with the added treatment. Still, it should be noted that due to lacking recommendations for SMT implementation, the chosen duration was arbitrary and might be too little to provoke any training effects.

Further difficulty arrises from the causality of the effects to SMT or SLIT rather than the actual physiotherapy sessions. Therefore, it was deemed important to record all therapies as detailed as possible. Therapists had specifically designed documentation sheets and patients were asked to maintain an exercise diary. High compliance (reported in chapter 5) allowed detailed examination of the applied therapies. From this data, a further satellite-project was initiated, where recorded therapies were qualitatively analysed and partitioned according to clinical relevant improvement in either of the primary outcome scores. This project was also not

part of the original work presented in this dissertation [35].

Using walking on treadmill as a comparator may also be viewed as contradicting, as similar postural training effects could be expected. Indeed, a recent study found low quality evidence that suggests walking is as effective as other non-pharmacological management methods at improving pain and function in adults with chronic low back pain [36]. For this reason, the duration and intensity was instructed at sub-effective levels [37].

Clinical implications

Clinical implications derived from the findings presented here are twofold: First, the role of SMT in musculoskeletal rehabilitation must be questioned. Although its value cannot be refuted, the repeated lack of convincing findings of benefits from SMT implementation may suggest that the way it has been used so far, should be reconsidered. It is clear that new standards and recommendations for the correct implementation must be provided to clinicians. Maintaining variability of the collective sensory input is the basis of the dynamics behind human movement, necessary for error compensation. Although it remains unclear whether SMT improves sensorimotor integration, the theoretical basis for it remains strong and merits its potential [38].

Second, the assessment of postural control in clinical settings must include multi-segmental analysis. Technical aids in musculoskeletal assessments will become more important in times where decisions have to be backed by reproducible methods. The development of new and more readily implementable as well as interpretable kinematic analyses have to be made more accessible to therapists and physicians. Hardbourne et al. describe a row of ways how non-linear measures of complexity could be used to monitor pathologic systems and refers to the medical field, which has already recognised the need for non-linear views on problems that affect multiple systems [39]. Non-linear analysis of gait, posture, and other movements can serve to more accurately identify aberrant features indicating subtle problems during development or neuropathic disease. In our postural control test, we only looked at one task, but for clinical assessments other functional tests may be of relevance and could be analysed using the UCM approach, e.g. myotome screening (walking on tip-toes and heels to identify weakness of ankle dorsiflexion, gait (e.g. subtle changes in Trendelenburg gait), etc. [40]

More effective treatments with short return-to-work times continues to be a priority in CNLBP research. Indirect costs, caused by work absenteeism or reduced productivity due to limitations, are still on the uprise [41]. It is well documented that the longer the patient is on sick leave, the less likely he or she is to return to work [42]. The earlier pain can be addressed effectively, the more likely a successful re-integration can be achieved for which reason CNLBP requires early and effective medical attention.

Implications for future research

More basic research on the field is required to identify minimum recommendations for practical instruction of SMT. This is true for healthy young adults, as well as for the elderly and for pathological conditions (e.g. musculoskeletal pain or neurodegenerative diseases with impaired balance). Once a theoretical framework for time, frequency, intensity, type, volume, pattern, and progression is available, large-scale effectiveness trials should try to compare more generalisable samples that allow subgrouping. As stated in chapter 2, interventions have to be reported with more care to important details which would allow comparison between such studies and strengthen their findings.

The observations of our research have led to the hypothesis that long-term pain may change motor control in a way that allows similar stability as in symptom-free people, but with a cost of excessive motion in several segments in order to compensate for rigidity in other areas. This hypothesis should be followed up in further studies. Moreover, higher firing rates in afferent receptors may not necessarily cause peripheral change or central motor re-learning [43, 44]. To provide evidence of the trainability of the sensorimotor system through balance training, it must be shown that acuity of sensory receptors and the signal conversion to and within the CNS can be enhanced [44]. More findings are needed showing in humans that the functional instability of joints can be addressed with SMT [43, 44, 45]. Other factors should also be considered, such as fear of falling, exact activity levels, or segmental proprioception. Also, in studies of CNLBP, economic factors should be considered, e.g. return-to-work times, days on sick-leave due to pain, amount of therapies visited, and cost-effectiveness of the investigated intervention[46]. Further longitudinal studies should inspect reproducibility of our findings to allow implications on how motor equivalence and individual joint contribution may change over time and with pain development. The effect of a postural specific intervention on both UCM variance and joint angle excursion would allow description of the direct link between pain, the applied intervention and postural control. Research on identification of sensitive biomarkers to subtle aberrations in patients with CNLBP and the design of effective treatments remain a high-priority in clinical research, as has been stated by the WHO [47].

Main original contribution

This dissertation contributes to the field of CNLBP rehabilitation and human movement science. It has identified relevant gaps in the existing literature, proposed a design for longitudinal pain studies, introduced new assessments to the field and has tested a widely accepted intervention method with unconfirmed effectiveness. Finally, it provides a broad discussion on the existing literature and offers suggestions for possible questions of future research and clinical implications.

The comprehensive qualitative data extraction and the concise summary of findings provided the first systematic literature review on SMT in musculoskeletal rehabilitation. It has shown

that there is no convincing evidence for the implementation of SMT in musculoskeletal rehabilitation, but outlines a row of theoretical considerations which warrant further investigations. The systematic review produced a major step forward and provides researchers of the field with an overview of existing literature which helps to narrow down research questions. For clinicians, it provides an accessible explanation as to why the findings so far must be considered with caution and that the effectiveness of SMT is yet to be confirmed. The published study protocol allowed other researchers in the field identify ongoing research. Open access study protocols serve as tools to promote transparency and prevent selective reporting bias. In an experimental step, the possibility to use novel non-linear kinematic assessments for applied clinical research was introduced. It is the first study that used dynamic multi-segmental analysis with the uncontrolled manifold approach in a cross-sectional study and for pre- to post assessments. The findings support current movements in gait and posture assessment for pathological conditions that claim linear outcomes of magnitude do not suffice to identify subtle motor control deficiencies. Finally, the randomised controlled trials delivered new evidence that suggest SMT may not be as effective as previously thought. Only few studies have compared SMT to active controls which is an crucial feature in the design if specific sensorimotor effects are to be attributed to SMT. In line with comparable studies, the question remains whether there is a specific added benefit of SMT compared to general exercise. Physiotherapists and exercise therapists may reconsider the way SMT is implemented to efficiently tailor their treatments to the needs of the patients and how progress may be assessed. The presented research on SMT provides a basis for researchers to develop further recommendations on dose and frequency guidelines for SMT and points out the still elusive role of postural control in CNLBP.

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Summary

This doctor thesis addressed the role of sensorimotor training (SMT) in chronic non-specific low back pain (CNLBP) rehabilitation and ways to assess postural control in a clinical setting. The aims were: (1) summarise existing literature on SMT in CNLBP rehabilitation, (2) to propose nonlinear assessment measures for motor control in patients with CNLBP, (3) and to test the effectiveness of SMT in a population of patients with CNLBP.

Chapter 1 provides a narrative review of the current understanding of chronic ($\geq$3 months) chronic non-specific pain and discusses ways it has been assessed in terms of changes in movement behaviour. CNLBP is a major cause for years lived with disability, particularly in developed countries. In the majority of low back pain cases, no specific organic cause can be identified which complicates treatments and frustrates patients. It has been suggested that patients with CNLBP exhibit aberrant movement behaviour which may be partly contributing to pain sustenance. It is believed that poor postural control and rigid movement patterns are caused by reduced perception of spatial orientation of the body's segments and faulty muscular activation patterns which in turn cause pain. In response to this theoretical model, a therapeutic intervention has been proposed, that is supposed to restitute normal muscle activation patterns through increased sensorimotor signalling, i.e. afferent proprioceptive firing rates and central nervous system processing for improved dynamical motor response. This so-called sensorimotor training and its role in musculoskeletal rehabilitation are at the core of this dissertation.

Chapter 2 systematically assesses the existing literature (1994 - 2013) on the effectiveness of SMT and its recommended implementation in CNLBP and chronic neck pain rehabilitation. All relevant electronic databases were searched from inception to February 2014. The methods followed the handbook for systematic reviews by the Cochrane Library and the PRISM statement for reporting systematic reviews. Only randomised controlled trials (RCT) comparing interventions with sufficiently described proprioceptive exercises compared to conventional therapies or inactive controls in patients with neck- or low back pain were included. Using the Cochrane Back Group assessment tool, two authors independently assessed each study for potentially relevant risk of bias. In accordance with the GRADE guidelines, the quality of evidence regarding the summary findings was rated as either very low, low, moderate or high, and accounted for risk of bias and other methodological short-comings.

Six of the 18 included studies focussed on neck pain while 12 of them addressed CNLBP.

The investigated interventions were categorised into three groups: Discriminatory perceptive exercises with somatosensory stimuli to the back (n = 2), multimodal exercises on labile surfaces (n = 13), and joint repositioning exercise with head-eye coordination (n = 3). Comparators entailed usual care, home based training, educational therapy, strengthening, stretching and endurance training, or inactive controls. The quality of the included studies was rated as low and RoB was deemed moderate to high. It was found that low quality evidence suggests SMT may be more effective than not intervening at all. Low quality evidence suggests that SMT is no more effective than conventional physiotherapy. Low quality evidence suggests SMT is inferior to educational and behavioural approaches.

The systematic review has shown that there are only few relevant good quality studies on SMT in CNLBP and chronic neck pain rehabilitation. A descriptive summary of the evidence suggests that there is no consistent benefit in adding SMT to neck- and low back pain rehabilitation and functional restoration. However, the evidence to refute the effects of SMT was just as low which reflects the lack of consensus regarding its value in musculoskeletal rehabilitation. From the scarce literature available, no recommendations regarding mode and doses of SMT implementation can be made.

Chapter 3 proposes procedures of a study trial to provide transparent reporting and publish ideas potentially useful to other researchers on the field. The study was presented a pilot study with a parallel, single-blinded, randomised controlled design.

Chapter 4 explores the potential of a novel assessment for postural control that takes into account the multi-segmental response to base of support perturbations. As poor postural control is often associated with CNLBP, the cross-sectional study compared 24 patients with CNLBP with 34 symptom-free controls. The study was an experimental attempt to describe postural control not only in terms of linear summary outcomes such as trajectories of centre of pressure (CP) trajectories, but to include the structure of the individual segmental contributions involved in postural control tasks. Linear summary outcomes do not sufficiently account for variance of movements, which is a key feature of healthy motor control. Complex systems, such as the human body, need variance to compensate errors and react to unpredicted changes in the environment. To do this, the study's primary goal was to describe the uncontrolled manifold (UCM) in a clinical setting. The UCM allows quantification of segmental variance as two sub-spaces: motor equivalent and non-motor equivalent variance. The latter sub-space represents undesirable variance which causes deviation from a particular movement task, e.g. stabilising the centre of mass (CM) over a certain base of support. Motor equivalent variance, on the other hand, indicates the amount of variance used to achieve the the targeted movement task. More relative amount of motor equivalence means more segmental movement was invested by the individual to maintain postural control. Traditionally, it has been viewed that patients with CNLBP have poorer abilities to maintain posture under perturbed circumstances, which would

be reflected in low levels of motor equivalent variance and higher relative levels of non-motor equivalence. However, our results suggest that long-term pain may lead to new motor control adaptation that allow normal stability at the cost of movement efficiency. The findings lend further support to the notion that summary outcomes do not suffice to describe subtle postural differences in CNLBP patients with low to moderate pain status.

Chapter 5 assessed the efficacy of a standardised SMT program as part of conventional physiotherapy in a randomised controlled trial. In a secondary analysis, it describes the limitations of the anticipated practicality of the uncontrolled manifold analysis in CNLBP assessment of postural control. Using the methods described in chapter 3, a RCT with 22 participants and two arms was conducted. During 4.5 weeks, all participants received nine standard physiotherapy sessions, one group with added SMT, the other with added sham exercise (sub-effective low intensity training). The outcomes were tested at baseline (BL) 2-4 days prior to intervention, pre- and post-intervention (T0, T1), and at four-week follow-up (FU) by a treatment blinded tester. Primary outcomes were pain and functional status while nonlinear measures were analysed for secondary analyses. Postural control was assessed with the same task applied in chapter 4. Despite significant improvement of ODI after SMT, overall findings of this study suggested that, in patients with moderate CNLBP, 9x15 minutes of added SMT as part of pre- scribed physiotherapy provides no added benefit for pain reduction, functional status improvement or change of postural control. It cannot be out-ruled that higher doses of SMT would be more effective and it should be kept in mind that results may not apply to patients with higher pain levels.

Chapter 6 discusses the results in light of other research in the field and lists a number of strengths and limitations as well as methodological considerations. The importance of SMT in musculoskeletal rehabilitation remains unclear as no convincing evidence for its effects could be uncovered. Conclusions drawn from comparable studies in the field are congruent with our findings, that there is only low quality evidence for the superiority of SMT over general exercise. Further implication for future research and clinical relevance are discussed. The experimental assessment of UCM outcomes must be further evaluated with more sophisticated instruments to assess psychometric properties of the measures. Before further intervention trials for SMT are warranted, clear guidelines based on dose-response studies should elucidate the mode of potentially effective SMT, i.e. its type, frequency, and dose.

In conclusion, we have shown that there is little scientifically reliable reason to assume that SMT would be beneficial for CNLBP rehabilitation. However, it is very likely that large-scale studies would have an important impact on our confidence in the findings and the estimated effects. Nonlinear assessment tools should be included in the evaluation of subtle changes of movement disorders, as they may help to explain group differences, or, as was the case of our

study, they may help to make sense of why there are no differences.

Zusammenfassung

Diese Dissertation befasst sich mit der Bedeutung sensomotorischer Trainingsmethoden (SMT) für die physiotherapeutische Behandlung von Patienten mit chronischen, nicht-spezifischen lumbalen Rückenschmerzen (CNLRS). Die Ziele der Arbeit waren: (1) Das Zusammentragen und Evaluieren bestehender Literatur über SMT in der Behandlung von CNLRS, (2) nicht-lineare Messmethoden für die Bewertung motorischer Kontrolle bei Patienten mit CNLRS vorzuschlagen und (3) die Wirksamkeit von SMT bei einer Studienpopulation mit CNLRS zu überprüfen.

Kapitel 1 fasst wichtige Aspekte des heutigen Verständnisses über die Verbreitung, Entstehung und Behandlung von CNLRS zusammen. CNLRS gilt als eine massgebliche Ursache für krankheitsbedingte Einschränkung der Lebensqualität, insbesondere in Industrienationen. Für einen Grossteil der Patienten, die wegen Rückenschmerzen behandelt werden müssen, lässt sich keine eindeutige organische Ursache erkennen. Dies erschwert Behandlungen und löst weitere Frustrationen bei Patienten und Patientinnen aus. Es wurde häufig beobachtet, dass Patienten mit CNLRS auffällige Bewegungsverhalten zeigen, welche für den anhaltenden Schmerz mitverantwortlich gemacht werden. Man geht davon aus, dass eine schlechte Haltung und steife Bewegungsmuster in dynamischen Situationen durch verminderte sensorische räumliche Wahrnehmung verschiedener Körpersegmente und fehlerhafte Koordinationsmuster muskulärer Aktivität ausgelöst werden. Aufgrund dieses theoretischen Modells, wurden zahlreiche therapeutische und präventive Trainingsmethoden entwickelt, die auf eine Wiederherstellung normaler Bewegungsmuster durch erhöhte sensomotorische Aktivität abzielen. In dynamischen Trainingssituationen sollen diverse Übungen die afferente Feuerungsrate erhöhen und dadurch die zentralnervöse Verarbeitung motorischer Signale verbessern. Dieses sogenannte sensomotorische Training steht im Zentrum dieser Abhandlung.

Kapitel 2 fasst systematisch die bestehende Literatur (1994 - 2013) über die Wirksamkeit von SMT und Empfehlungen für dessen Einsatz in der Behandlung von CNLRS und chronischen Nackenschmerzen zusammen. Alle relevanten elektronischen Datenbanken wurden von deren Gründungsdatum bis Februar 2014 durchsucht. Die entsprechende Vorgehensweise folgte den strikten Anforderungen des Cochrane Handbuchs für systematische Literaturarbeiten und den PRISM Empfehlungen für die Beschreibung der Methoden. Nur randomisierte Kontrollstudien, die eine klar beschriebene SMT-Methode enthielten und diese mit konventioneller Therapie oder inaktiven Kontrollgruppen verglichen, wurden für die qualitative Auswertung eingeschlossen. Mittels dem Bewertungsbogen der 'Cochrane Back Group' wurde das Risiko möglicher Datenverzerrungen bewertet. Die methodologische Qualität und die damit zusammenhängende Qualität der Resultate wurde mit dem GRADE verfahren bewertet. Die Qualitt

der zusammengefassten Resultate wurde entsprechend als "sehr niedrig", "niedrig", "moderat", oder "hoch" eingestuft.

Sechs der insgesamt 18 eingeschlossenen Studien untersuchten Nackenschmerzen, die restlichen 12 untersuchten CNLRS. Die evaluierten Interventionen wurden in drei Gruppen kategorisiert: Diskriminatorische perzeptive Übungen mit somatosensorischer Reizen am Rücken (n=2), multimodale Übungen auf labilen Unterlagen (n = 13) und Repositionierungsübungen mit okkulomotorischer Koordination (n = 3). Die Kontrollgruppen erhielten Standardbehandlungen, Heimübungen, edukative Therapien, Kraft-, Dehnungs-, und Ausdauertraining, oder gar keine Intervention. Die Qualität der eingeschlossenen Studien wurde als niedrig beurteilt und das Risiko einer Datenverzerrung als moderat bis hoch. Resultate mit niedriger Qualität deuten darauf hin, dass SMT zwar wirksamer ist als gar nicht zu intervenieren, aber nicht wirksamer als normal Therapie ist und gegenüber edukativen Ansätzen gar weniger wirksam zu sein scheint.

Die systematische Literaturarbeit konnte zusammenfassend aufzeigen, dass bisher nur wenige methodologisch unbedenkliche Studien zur Wirksamkeit von SMT in der Behandlung von Patienten mit CNLRS und chronischen Nackenschmerzen durchgeführt wurden. Eine qualitative Beschreibung der bestehenden Evidenz lässt vermuten, dass SMT keine eindeutigen Vorteile gegenüber allgemeiner Aktivität bringt. Allerdings ist die Beweislage, um die Wirksamkeit von SMT insgesamt zu widerlegen ebenfalls sehr dünn. Aus der eher beschränkten Auswahl an wissenschaftlicher Literatur, können bisher keine Empfehlungen über die Anwendbarkeit und den Einsatz von SMT gegeben werden.

Kapitel 3 beschreibt die geplante Vorgehensweise für die Patientenstudie. Dies ermöglicht transparente Einsicht in die Vorgehensweise, was für andere Forscher auf dem Gebiet von Interesse sein kann. Des Weiteren verhindert es, dass selektiv nur positive Resultate berichtet werden. Die Studie wurde als Pilotprojekt mit parallelem, einfachblindem, randomisiert kontrolliertem Design beschrieben.

Kapitel 4 untersuchte die Möglichkeiten neuer Mess- und Analysemethoden zur Bewertung der posturalen Kontrolle. Schlechte Haltungskontrolle wird häufig mit CNLRS assoziiert, weshalb diese Querschnittsstudie 24 Patienten mit 34 schmerzfreien Probanden bezüglich Haltung verglich. Die Studie sollte die posturale Reaktion der Probanden nach einer ausgelösten Pertubation auf einer labilen Plattform erfassen und dabei eine multi-segmental Auswertung zulassen. Die Studie war ein experimenteller Versuch die Haltung durch nicht-lineare Parameter zu beschreiben, die die einzelnen Gelenkssegmente miteinschliessen. Diese Methode soll im Gegensatz zu traditionellen linearen Paramtern, wie die Auslenkung des Druckmittelpunktes, die Varianz der Bewegung besser berücksichtigen. Komplexe Systeme, wie es der menschliche Körper ist, benötigen Varianzen um unvorhergesehene Änderung der Umgebung besser zu kompensieren. Das primäre Ziel der Studie war demnach, die "Uncontrolled Manifold (UCM)" Analyse in einem klinischen Umfeld zu testen. Die UCM-Methode erlaubt es,

die beobachtete Varianz in einer Bewegung in bewegungsäquivalente und und bewegungsabweichende Varianz zu unterteilen. Letzteres beschreibt Varianz die zu unerwünschter Abweichung vom Bewegungsziel führt, in unserem Fall die Bewahrung des Körpermassenmittelpunktes über der Unterstützungsfläche. Im Gegensatz dazu ist die bewegungsäquivalente Varianz ein Indikator für Varianz die zur Erhaltung eines bestimmten Bewegungsziels beiträgt. Entsprechend deutet eine höhere bewegungsäquivalente Varianz auf stabilitätserhaltende Bewegung der individuellen Segmente hin. Heute geht man davon aus, dass die eingeschränkte posturale Reaktionsfähigkeit bei Patienten mit Rückenschmerzen durch eine höhere relative bewegungsabweichender Varianz widerspiegelt würde. Unsere Resultate deuten aber darauf hin, dass lange andauernde Schmerzen bei CNLRS Patienten zu Anpassungen im motorischen System führen, die auf Kosten effizienter Bewegungsabläufe normale Stabilisierungsfähigkeiten zulassen. Das heisst, der Körpermassenmittelpunkt konnte nur durch starke Schwankungen des Hüft- und Kopfgelenkes stabilisiert werden, was sich in einer höheren Bewegungsäquivalenter Varianz widerspiegelte. Die erhöhten Gelenksauslenkung bei den Patienten war moderat positiv mit Schmerzintensität und Funktionseinschränkung korreliert. Die Resultate liefern weitere Belege dafür, dass Parameter die auf lineare Summation basieren, nicht ausreichen um subtile posturale Veränderungen bei CNLRS Patienten zu erkennen.

Kapitel 5 beschreibt die Untersuchungen zur Wirksamkeitsprüfung eines standardisierten SMT Programms als Teil konventioneller Physiotherapie bei Patienten mit CNLRS. In der randomisierten Kontrollstudie, dessen Design in Kapitel 3 beschrieben wurde, wurden subjektive Schmerzparameter und der funktionelle Status erfasst. In einer sekundären Analyse wurden die Grenzen der praktischen Anwendung des UCM untersucht. Insgesamt 22 Patienten konnten eingeschlossen werden und in eine der beiden Studiengruppen eingeteilt werden. Alle Teilnehmer erhielten die gleiche Dauer an konventioneller Physiotherapie. Eine Gruppe erhielt zusätzliches SMT während die andere ein sub-effektives Ausdauertraining niedrigere Intensität erhielt. Die Ausgangswerte der Messparameter wurden 2-4 Tage vor Beginn der Therapien erfasst. Danach kurz vor und direkt nach der Interventionsdauer von 4.5 Wochen, bzw. nach 9 Therapien (T0 und T1). Schliesslich wurde eine Nachfolgeuntersuchung vier Wochen nach den Therapien durchgeführt. Alle Untersuchungen wurden von einem bezüglich Gruppenzuteilung uninformierten Tester durchgeführt. Trotz signifikanter Verbesserung der funktionellen Werte nach SMT, deuteten die Ergebnisse insgesamt darauf hin, dass Patienten mit moderaten CNLRS keine zusätzlichen Verbesserungen verspüren als ohne ein wirksames Zusatztraining. Es kann jedoch nicht ausgeschlossen werden, dass höhere Dosen des SMT eine höhere Wirkung zeigen würde. Ausserdem sollte beachtet werden, dass diese Resultate womöglich nicht auf Patienten mit höheren Schmerzen zu übertragen sind.

Kapitel 6 diskutiert die Resultate im Kontext anderer Studien des Forschungsgebietes und listet die Stärken sowie die Schwächen unserer Studien auf. Die Bedeutung von SMT in musku-

loskeletaler Rehabilitation ist weiterhin unklar, da nach wie vor keine überzeugende Resultate für dessen Wirksamkeit sprechen. Unsere Schlussfolgerung, dass nur ungenügend Hinweise auf den zusätzlichen Nutzen von SMT vorliegen, decken sich weitgehend mit denjenigen der anderen Studien, die ähnliche Vorgehensweisen beschrieben haben. Des Weiteren wird diskutiert, welche Richtungen zukünftige Forschungsprojekte auf diesem Gebiet einschlagen könnten. Die experimentelle Anwendung der UCM-Methode bedarf weiterer Evaluation und sollte auf Verlässlichkeit überprüft werden. Bevor weitere Interventionsstudien für SMT angebracht wären, sollten Richtlinien basierend auf Dosisstudien erstellt werden. Dadurch können Empfehlungen zur Dauer, Intensität und Art des Trainings berücksichtigt werden.

Abschliessend können wir sagen, dass nur ungenügend wissenschaftliche Evidenz den Nutzen von SMT in CNLRS Therapien unterstützt. Die Beweislage ist allerdings von niedriger Qualität, was bedeutet, dass neue Studien mit grösseren Studienpopulationen diese Schlussfolgerung ändern könnten. Nichtlineare Messmethoden könnten zukünftig eingesetzt werden um subtile Abweichungen und Veränderungen zu erkennen, was die Früherkennung und Beobachtung von verschiedenen Bewegungsstörungen ermöglichen könnte. In unserem Fall, halfen sie zu erkennen weshalb erwartete Unterschiede nicht bestätigt werden konnten.

Acknowledgments

In the course of writing my dissertation, and finally completing it, I have come to learn two things about succeeding such a mammoth project. First, it could not have been done without the help of enthusiastic and intelligent people around me. Thus, the first part of this section is dedicated to all the people who have helped me realise and bring to an end what initially looked like an unsurmountable challenge.

First, and foremost, I would like to thank my mentor and co-supervisor, Dr. Corina Schuster-Amft. You have been an incredible source of optimism and motivation and I can quite bluntly say that without your support this whole project would not have been possible in the first place. The way you promoted me from student to post-graduate to doctoral student has given me the necessary confidence to embark on this odyssey with uncertain outcome. You are a visionary therapists who has greatly contributed to the evidence based treatments, bridging disciplines from health care providers and acknowledge the importance of human movement sciences in therapy research. Also for this I would like to thank you and look forward to our next projects.

Next, I would like extend my deep gratitude to PD Dr. Eling D. de Bruin for taking me on as his doctoral student. I was ever so grateful for your methodological advice and support in other matters. There is a way about you, that simply sheds new light on difficult topics and make it seem 'doable'. I have fond memories of congress meetings and seminaries where cracking a joke came as easy to you as did the explanation of simple solutions to complex problems. To the point and concise and always looking out for opportunities for your students. Thank you for a great time and I look forward to more exciting projects with your group.

Working in the background but there from the beginning was my co-author Brigitte Wirth who had supervised me during my Master studies. Many thanks for believing in me and for your valuable contributions to our publications. Your critical point of view from a therapist's perspective with many years of clinical research experience always filled the gaps in the articles we wrote together. I thoroughly enjoyed working with you and genuinely hope there will be more opportunities to do so.

I remember the first meeting with my co-supervisor, Prof. Nicole Wenderoth, at her office, only a few weeks after she joined the department. What was intended to be a proposal for co-supervision turned out to be an inspiring conversation about possible methods and further questions we could pursuit with our research. I was lucky to have such an experienced and distinguished researcher on neuromotor control in my team and greatly benefited from our meetings. Your critical remarks and intelligent advise has helped methodologically and theoretically

strengthen the final procedures. I would like to thank you for your uncomplicated support and enthusiasm for topics outside of your field. Many thanks also to Prof. Wolfgang Taube, who on very short notice agreed to act as co-examiner.

I wish to extend my gratitude to Prof. Dr. Thierry Ettlin, Medical Director, and Mr. Matthias Mühlheim, Administrative Director, at the Reha Rheinfelden for their continuous support of and belief in the clinic's research department. It takes foresight to invest into what might be of relevance tomorrow and is a bold step forwards toward evidenced based medicine. I would also like to thank Prof. Ettlin for his valuable contributions in clinical considerations regarding the patient studies.

To bridge the gap of my lacking clinical experience with patients, I vastly relied on the expertise and the excellence of the therapists and physicians at the clinic. I had the privilege to work with two different research assistants with clinical backgrounds and I would like to thank Andrea Henneke and Zorica Suica for their professional counsel, their endless help with data quality monitoring and video editing, and their friendship which grew during our rare coffee breaks. From the physiotherapy department, the valuable discussions with Sabrina Naegelin, head of the out-patient department, with Felix Mauch, and Christian Seibt were extremely helpful to maintain the clinical relevance of our investigations and make sense of our findings. Special thanks also to further treating therapists Pamela Spengler, Michaela Zimmermann and Astrid Simon for their enthusiastic support during the intervention phases. Dr. Christoph Müssig was strongly involved during the screening phase and clinical examination of all patients and I would like to thank him and his team for their uncomplicated support in this matter. Of course many more therapists were in some way confronted with the study and I thank them for tolerating and promoting the project.

Several students were involved in satellite-projects of this dissertation. I wish to thank Vivien Gnehm and Maria Emmert, who contributed to the assessments during their Master thesis and Sophie Mandl, who analysed the therapy contents for her thesis. Also, Michelle Anliker, and Michael Preiswerk significantly increased the reliability of the motion tracking setup during their research practicals at our clinic and should also be acknowledged. For the technical support from the supplier of measurement device, I would like to thank Yves Hess and Erwin Schweizer who have become more than just business partners.

I would like to thank my peers at the institute of Human Movement Sciences for their valuable inputs during our monthly PhD round table meetings. Particularly Corinna Gerber, Frederico Genaro and Alexandra Schättin. Similarly, the research department at the Reha Rheinfelden held bi-monthly meetings which were an indispensable source for statistical and clinical feedback. Special thanks to Dr. Frank Behrendt, Willi Bäckert, Doris Felber, Dr. Markus Stöcklin, and Prof. Kenneth Hunt. In the course of this project, many students involved in other projects were part of the team and their inputs were highly appreciated, especially from Rahel Gerber, Michael Grill, Szabina Koppel, Christine Wondrusch, Ludwig Schmid, Heike Rosemeyer and Stephanie Hellweg. Some former members of the group have also supported and encouraged me,

especially Dr. Oliver Stoller and Dr. Jittima Saengsuwan.

Finally, I would like to express my gratitude to all patients and volunteers who so enthusiastically participated in all our trials.

The second thing I learned is, that succeeding in one part comes with failing in another. In this case, it was failing to be the friend, the brother, the son, the husband and especially the father I would have liked to have been. This sounds ever so dramatic, but I must admit that during the last 12 months of this thesis I have neglected parts of my life that define parts of my personality. The reason I write about this in the acknowledgement is because I would like to thank my friends, my siblings, my mother, my wife, and my son for giving me the liberty to pursuit my plans. I would like to thank my friends for encouraging me and generally giving me a good time when most needed. Particular thanks to Sandro, because it was him who guided me in a moment of lost perspectives. Then I would like to thank Markus, who always knew how to reach me while I was buried beneath heaps of books in the cellars of our clinic. You always reminded me of true male friendship and always knew when it was time to enjoy a sip of the good old Scotch, to celebrate or to cheer up. Finally, I would like to thank my family member and their spouses for their continuous support: Alison for her daily quotes of a better world, Anna for her ability to see both sides of things, Matthew for teaching me how to iron a shirt, Mum and my parents in law, for your support with our boy, particularly in the final months.

I just got off the phone with my wife, who has headed off to see her parents with Donavan, our son, to give me space and time to complete these last lines. Without you Sina, I would not have had the strength, the will, nor the capacity to go through with it.